VOLUME 13
NUMBER 5
MAY, 1960

ORAL SURGERY
ORAL MEDICINE
and ORAL PATHOLOGY

# OPERATIVE ORAL SURGERY

## ODONTOMA OF THE MAXILLA

*Louis W. Schultz, D.D.S., M.D.,* and*
*Sunder J. Vazirani, D.D.S., D.O.S., M.S., F.I.C.D.,** Chicago, Ill.*

AN ODONTOMA is a benign tumor arising from the abnormal growth of cells of the enamel organ or remnants of the dental lamina. It may consist of enamel, dentine, cementum, pulp, fibrous tissue, and bone arranged in an irregular manner.

These tumors may be of considerable size and cause swelling of the jaw visible on examination. They sometimes remain quiescent for years and go undiagnosed. Often the neighboring teeth erupt in irregular positions, with abnormally large spaces interproximally caused by the missing tooth or teeth which formed the tumor.

Odontomas are often formed from the deciduous or permanent tooth germ. Upon discovery, they should be promptly removed to prevent malocclusion of the permanent dentition. It is not uncommon to find normal eruption of the permanent teeth prevented by an odontoma. Whenever there is a missing permanent tooth or retention of a deciduous tooth, routine intraoral roentgenograms should be made to rule out oral pathology. Being benign, odontomas should be removed by conservative treatment.

Odontomas may be solid or cystic. They occur in young persons and are more common in the mandible than in the maxilla. They are generally discovered, and are recognized readily, by routine roentgenographic examination.

This article reports a case of maxillary odontoma successfully treated. A step-by-step description of the surgical technique employed in the removal of the odontogenic tumor is illustrated.

From the Department of Surgery, Division of Oral Surgery, Research and Educational Hospitals, University of Illinois.
*Clinical Associate Professor of Oral and Maxillofacial Surgery.
**Formerly Instructor in Oral and Maxillofacial Surgery and Assistant in Anatomy. Present address: Arthur House, 11 Cooperage Rd., Bombay, India.

CASE REPORT

*Chief Complaint.*—J. S. was a 13-year-old white boy who, on Nov. 15, 1956, was presented at the Research and Educational Hospitals for orthodontic treatment.

*Present Illness.*—In January, 1950, the patient's parents noted irregularities of the anterior upper teeth. The condition had progressed during the past six months (Fig. 1).

Fig. 1.—Preoperative view of the maxilla.

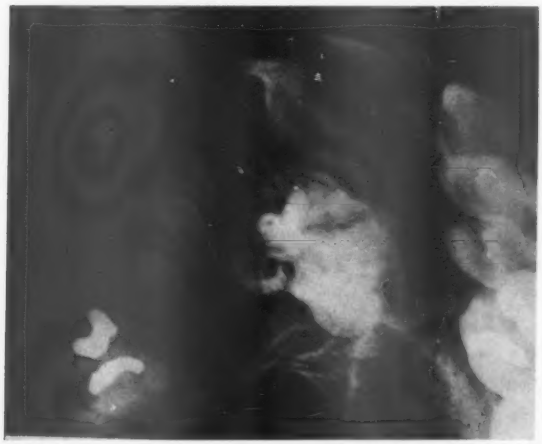


Fig. 2.—Preoperative occlusal roentgenogram reveals a roentgenopaque, well-defined mass in left canine fossa.

*Past History.*—The patient's deciduous teeth were extracted at various periodic intervals. Periapical roentgenograms of the teeth had never been taken. The eruption time of the permanent dentition was within normal range.

*Oral Examination.*—The examination at this time revealed an irregularity of the anterior upper arch with slight overlapping of the upper central incisor teeth and anterior traumatic bite. The left maxillary deciduous canine was still in place and very firm; the permanent canine was missing (Fig. 1).

*Laboratory Data.*—Laboratory studies revealed a hematocrit of 41.0 per cent and a white blood count of 14,400. Urinalysis revealed a specific gravity of 1.012. Serology was negative.

*Roentgenographic Findings.*—In the routine roentgenographic examination, a cluster or conglomerate mass of tooth structure, within a sharply defined environment, was noted in the periapical region of the left upper (|123) teeth. The apices of the incisors were in close relation to this structure (Fig. 2). The occlusal view of the maxilla showed a roentgenopaque, well-defined mass in the left canine fossa measuring 1.0 by 1.5 cm. in diameter.

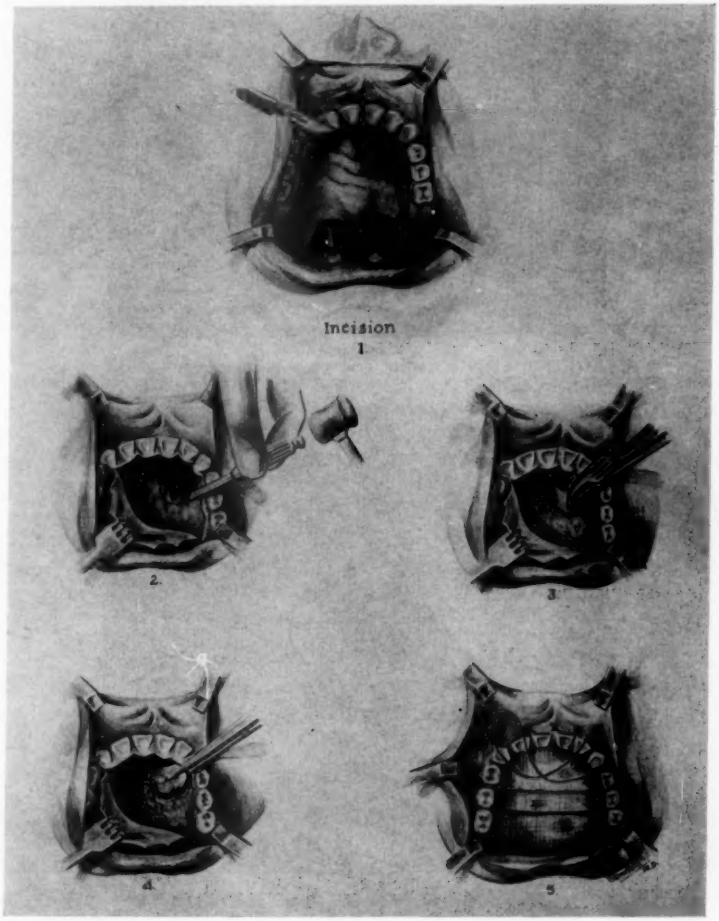



Fig. 3.—A step-by-step surgical technique.

*Roentgenographic interpretation:* Odontoma in the left canine fossa formed from the permanent tooth germ.

*Treatment and Course.*—The patient was admitted to the hospital for surgical enucleation on Nov. 28, 1956. The complete physical examination was essentially normal, except that

the patient had a roentgenopaque mass in the left canine fossa. The teeth responded to heat, cold, and electric pulp tests.

On Nov. 30, 1956, after premedication with 25 mg. of Demerol and 0.4 mg. of Scopolamine, the patient was taken to the operating room. Following induction of nasotracheal anesthesia (nitrous oxide plus ether), he was prepared and draped in the usual manner.

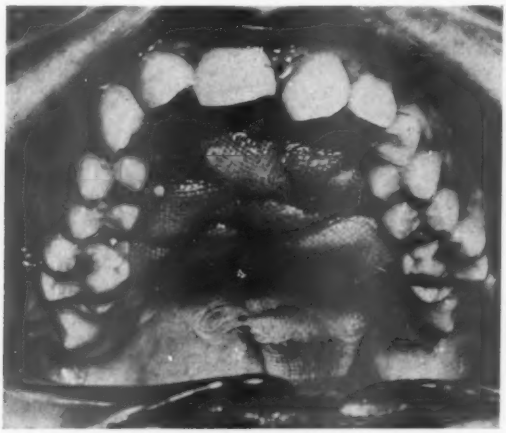
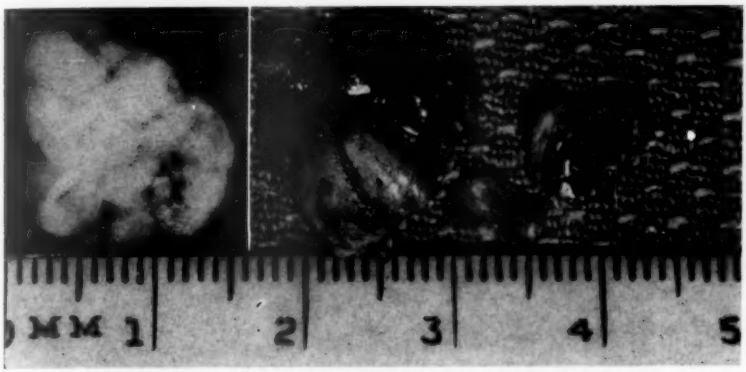


Fig. 4.—Photograph showing oral pack as a pressure dressing.

Fig. 5.—Postoperative roentgenogram of the palate.

The mouth was opened with a mouth gag, and an oropharyngeal pack was placed in the throat. An incision was made with No. 15 Parker blade along the gingival margin, extending from the right second maxillary incisor on one side to the second molar on the other (Fig. 3, *1*). With a sharp periosteal elevator, the mucoperiostetum was detached from the bone and retracted so that a sufficient part of the palate was exposed to permit ready access to the tumor. The vessel emerging from the incisive foramen was severed and ligated with 0000 plain catgut. The bone covering the tumor was thin and perforated in the center.

A sharp chisel and rongeur forceps were used to remove the bone until the tumor was exposed (Fig. 3, *2* and *3*). The tumor was removed with periosteal elevators for pathologic examination, which was consistent with odontoma. It was encapsulated with fibrous connective tissue (Fig. 3, *4*). Resorption of the root apex of the left lateral incisor was noted. The cavity was inspected and found to be completely denuded of tumor and fibrous membrane.




*A.* *B.*

Fig. 6.—Gross specimen (*B*) demonstrates encapsulated mass, consistent with odontoma. *A* shows radiographic view of the specimen.

Fig. 7.—Photomicrograph of complex odontoma.

The palatal mucosa was returned to its normal position and sutured to the labial gingival mucosa with 00000 Dermalon. Petrolatum gauze was placed over the wound as a pressure dressing and maintained with braided silk placed interdentally (Fig. 3, *5*). The patient tolerated this procedure very well and was sent to the recovery room in good condition. Approximate blood lost was 125 c.c.

The postoperative treatment consisted of the following: (1) administration of Abbocillin, 600,000 units daily for four days; (2) 25 mg. of Demerol every four hours for pain only; and (3) a liquid diet for the first twenty-four hours, to be changed to a soft diet as tolerated. The immediate postoperative course was uneventful except for a sore throat (due to the nasotracheal tube) for three days.

On the fourth postoperative day, the oral pack was removed (Fig. 4). Irrigations with a saline solution were continued until the wound had completely healed. The patient was discharged from the hospital on the fifth day (Dec. 5, 1956).

The patient was seen as an outpatient two weeks later. The wound appeared to be healing normally. The sutures were removed, and the postoperative roentgenograms were made.

*Postoperative x-ray report:* "The occlusal film following removal of odontoma from the left maxillary area shows apparently complete removal and no evidence of recurrence or postoperative complications." (Fig. 5.)

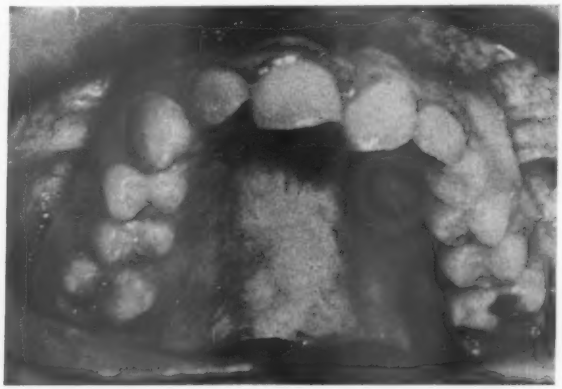


Fig. 8.—Postoperative view showing complete healing of the soft tissue.

*Pathologic Findings.—*

*Gross description:* Specimen A consisted of an oval, calcified mass with an irregular surface, measuring 15 by 14 by 14 mm. (Fig. 6).

Specimen B consisted of approximately twelve fragments of bone spicules, the largest measuring 20 by 5 by 7 mm.

*Microscopic description:* Sections from specimen A showed a crescent-shaped collar of vital lamellated bone surrounding a mass of calcified tissue. This mass consisted of irregularly arranged masses of cementum, irregular dentine, and enamel matrix. Between and within them were irregular calcifications (Fig. 7). *Diagnosis:* Complex odontoma.

The fragments of bone in specimen B consisted histologically of mature bone containtaining osteocytes in the lacunae and showing apposition and in some places resorption. The marrow spaces were filled with fibrous marrow. *Diagnosis:* Normal bone.

*Follow-up.*—The patient was followed periodically in the outpatient clinic for one year (Dec. 21, 1957). There was no evidence of recurrence of the tumor. The patient was tentatively discharged from the oral surgery clinic and was referred to the orthodontics department for further care (Fig. 8).

# MIXED TUMOR OF THE SALIVARY GLANDS OF THE MANDIBLE

## Report of a Case

*Oscar Hoffer, M.D.,* and Giorgio Vogel, M.D., Milan, Italy*

MIXED tumor of the salivary glands, localized in the mandible and presenting as primary tumor, is a very rare lesion. In an examination of the literature, we have found only six cases.[1, 4-6, 8, 9] According to our views, two of these cases (those reported by Rosenthal[8] and Malan[4]) did not have the histopathologic requisites necessary for the diagnosis of mixed tumor of the salivary glands. Actually, both lesions were made up of tissues of mesenchymal origin, and no epithelial tissues were present.

This localization of mixed salivary gland tumor is of interest because of its rareness and because of the frequent mistakes made in its diagnosis.

### CASE REPORT

M. R., a 32-year-old white woman, was admitted to the Institute on Sept. 11, 1957. Four months earlier her lower right second molar had been removed. Following the extraction, there was a discharge of purulent material from the socket for several days. This was accompanied by swelling. The antibiotic therapy administered by the patient's dentist was inefficient. An intraoral x-ray film disclosed an embedded lower third molar and a large rarefied area. For these reasons, the patient was referred by her dentist to our clinic.

The patient's medical history was essentially negative, and the family history was noncontributory.

Physical examination on admission revealed a bulging of the buccal mucosa in the region of the lower right third molar. Palpation of the enlarged area revealed no crepitation or fluctuation. The swelling was of small size, hard, and moderately painful.

*Roentgenographic Examination.*—A right lateral roentgenogram of the mandible was taken. The angle and ramus of the right mandible appeared changed as to both shape and structure. There were multiple radiolucent, rounded areas partially superimposed and intersected by bony trabeculae altering the normal structure of the spongiosa. The bone of the ascending ramus showed a marked expansion and a thinning of the cortex. The boundaries of the lesion were definite and surrounded by normal tissue. The outlines were moderately expanded. At the posterior end of the horizontal ramus the boundary of the cavities was much less definite. The area presented a hazy, fuzzy appearance, which differentiated it from a true cystic lesion. In the middle of the region of the angle was the impacted lower right third molar. Its roots were resorbed (Fig. 1).

*X-ray diagnosis:* Multicystic ameloblastoma.

---

From the Departments of Oral Pathology and Oral Surgery of the Dental Institute, Medical School, University of Milan.

*Director of the Dental Institute, Medical School, University of Milan.

*Operation.*—Following induction of general endotracheal anesthesia with Pentothal sodium, a gingival incision was made, extending from the lower right second premolar to the trigone region and along the ascending ramus. The mucous membrane was retracted, and the masseter and pterygoid muscles and the ascending ramus were exposed. Here a large mass which occupied the largest part of the ascending ramus became visible.

The impacted third molar was extracted, and the cystic mass was entirely enucleated. The cavity was débrided, and its floor was electrocoagulated. The mucoperiosteum was returned to its proper position and sutured into place with silk. The patient was given procaine penicillin.

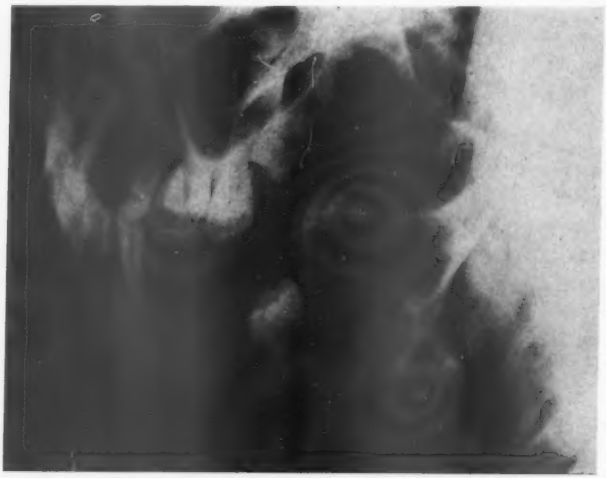


Fig. 1.—Lateral roentgenogram of right mandible.

*Operative diagnosis:* Multicystic ameloblastoma?

The postoperative course was favorable, and penicillin therapy was continued for three additional days. Deep roentgenotherapy was instituted.

*Histopathologic Examination.*—The specimen consisted predominantly of newly formed epithelial tissue which appeared organized as solid masses of glandular structures (Fig. 2). These showed a tendency to cystic transformation (Fig. 3). In some instances this cystic evolution was much accentuated and showed papillary ingrowths. Into and between the cystic dilatations a mucoidlike material was seen; this was a secretion derived from the epithelial cells. This material stains red-violet with PAS stain and deep blue with Alcian blau. The connective tissue of the stroma shows some evidence of a hyperplastic process. In the specimen examined, we found no sign of malignancy, but there was some tendency to epidermoid metaplasia.

*Diagnosis:* Papillary cystic mixed tumor.

## CONCLUSIONS

Two important facts must be remembered in connection with this tumor: (1) It was quite impossible to make any definite roentgenographic diagnosis, and the same difficulty was present at the operating table. (2) Considering the microscopic pattern, these neoplasms are too frequently classified as benign

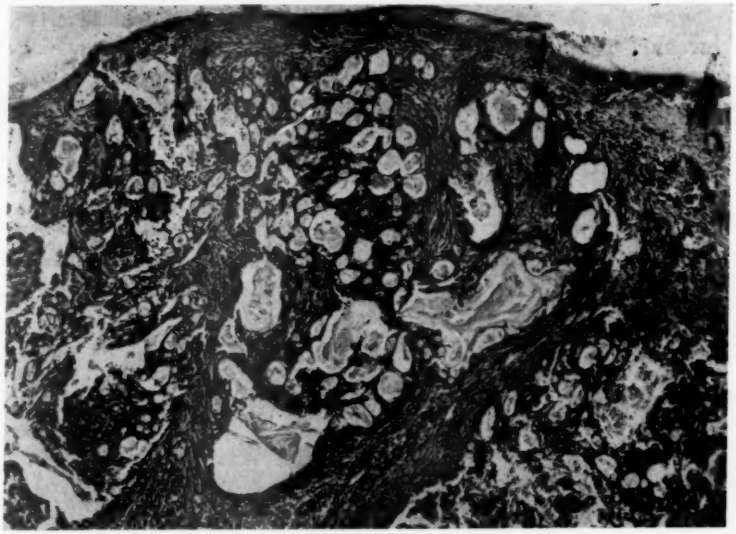


Fig. 2.—Low-power section of mixed tumor of mandible. (Magnification, ×45.)

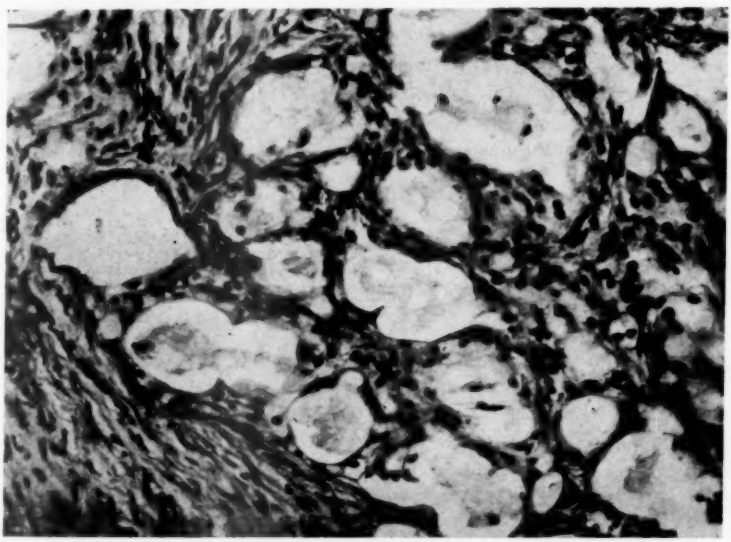


Fig. 3.—Higher magnification of specimen shown in Fig. 2, demonstrating cystic evolution of the tumor epithelial tissue. (Magnification, ×200.)

tumors. Our clinical and surgical experience, however, demonstrates that these tumors, even though they are histologically benign, have a characteristic tendency not only to recur in loco but also to metastasize. The frequency of metastasis is 10 to 12 per cent. The diagnosis, therefore, must be made exclusively from the histologic findings, and the surgical treatment must be radical and combined with deep roentgenotherapy.

REFERENCES

1. Burford, W. N.: Symposium on Eighteen Cases of Benign and Malignant Lesions of the Oral Cavity, Am. J. Orthodontics & Oral Surg. 33: 1, 1947.
2. Bumsted, W. D.: Cylindroma of the Mandible, ORAL SURG., ORAL MED. & ORAL PATH. 8: 546, 1955.
3. Leonardelli, G. B., and Vogel, G.: Aspetti istochimici dei cosidetti tumori misti, Gior. ital. patol. e scienze affini 5: 1, 1958.
4. Malan: Dei tumori intramurali palatini, Arch. ital. laring. 51: Supp. 11, 1958.
5. Morgan, J. G., and Thoma, K. H.: Mandibular Mixed Tumor of the Salivary Type, Am. J. Orthodontics & Oral Surg. 26: 602, 1940.
6. Neuhaus, N.: Mischtumoren des Unterkiefers, Dissert. Köln., 1936.
7. Pizzetti, F., and Leonardelli, G. B.: Sui tumori misti dell'estremo cefalico (con particolare riguardo alle localizzazioni extraparotidee), Tumori 36: 136, 1950.
8. Rosenthal, W.: Beitrag zur Wiederherstellungschirurgie nach Kieferresektion und Nekrose, Arch. klin. Chir. 141: 248, 1927.
9. Stoll, H. C., Marchetta, F. C., and Schobinger, R.: Malignant Epithelial Tumors of the Mandible and Maxilla, A. M. A. Arch. Path. 64: 239, 1957.
10. Thoma, K. H.: Oral Pathology, ed. 4, St. Louis, 1954, The C. V. Mosby Company.
11. Thoma, K. H., and Goldman, H. M.: Odontogenic Tumors: A Classification Based on Observation of Epithelial, Mesenchymal, and Mixed Varieties, Am. J. Path. 22: 433, 1946.

# ODONTOGENIC CYST OF THE MANDIBLE

*Louis W. Schultz, D.D.S., M.D.,* Robert A. Atterbury, B.S., D.D.S., F.I.C.D.,** and Sunder J. Vazirani, D.D.S., D.O.S., M.S., F.I.C.D.,*** Chicago, Ill.*

THE responsibility for the diagnosis and treatment of odontogenic cysts involving the jaws belongs to the oral surgeon. Because of his advanced studies in the anatomy, physiology, pathology of the oral tissues, he possesses additional technical knowledge pertaining to the jaws.

Cystic growths of odontogenic origin involving the maxilla and mandible may form extensive tumor masses. The degree of extension, the size of the growth, and the involvement of adjacent structures depend on the duration of the growth and the amount of stimulus applied to it. The most commonly occurring cyst is of the radicular group.

Several methods of treatment have proved satisfactory. These include enucleation and dressing of the cyst cavity until healing has approached the surface, Partsch's operation, enucleation of cystic contents and immediate bone grafting, radical resection of the mandibular portion, and complete enucleation and primary closure. Some authorities believe that the cyst cavity may be obliterated by using Gelfoam or bone bank chips. We see no reason to add foreign material to healthy tissues.

In dealing with such cysts, we prefer complete enucleation of the cystic lesion with suturing. We have achieved excellent results with this method. We do not believe in prolonged treatment in radical resection, or in subjecting the patient to a drastic operation such as bone grafting.

A report of an extensive, large radicular cyst of the mandible which was diagnosed by histologic examination and treated successfully by conservative primary surgical enucleation follows. This is an example from the series of cases which we have treated.

## CASE REPORT

A. C., a 60-year-old white woman, came to the oral surgery clinic on Nov. 4, 1955, for treatment of a swelling of the right side of her face.

*History of Present Illness.*—The patient stated that approximately six weeks previously her right lower lateral incisor had been extracted under local anesthesia because of infection.

---

From the Department of Surgery, Division of Oral Surgery, Research and Educational Hospitals, University of Illinois.

*Clinical Associate Professor of Oral and Maxillofacial Surgery.

**Assistant Professor of Oral and Maxillofacial Surgery.

***Instructor in Oral and Maxillofacial Surgery and Assistant in Anatomy; at present Head and Assistant Professor, Dental Department, Christian Medical College, Ludhiana, Punjab, India.

One week later a swelling developed in the right jaw. The swelling was treated with hot packs and penicillin, but there was no definite response to this therapy. Finally, the patient was seen by a family physician who diagnosed the swelling as a tumor of the right mandible.

*Past History.*—The past medical history revealed that the patient had undergone bladder surgery about eighteen years earlier. Family and personal histories were essentially negative.

*Clinical Examination.*—The patient, who was well developed and well nourished, was very cooperative and pleasant. She did not appear to be in acute distress. A complete physical examination was essentially normal. Examination of the head and neck revealed a slight swelling of the right mandible. The patient was partially edentulous and had lower anterior teeth. The mucous membrane of the mouth appeared normal. A localized hard swelling, with no signs of inflammation, could be felt on digital examination. The enlargement conformed to the buccal curvature of the mandible in the retromolar area. The patient had no symptoms of paresthesia.

Fig. 1.—Preoperative anteroposterior view of the mandible on Nov. 6, 1955. Note large, well-circumscribed radiolucent lesion in the right mandible.

*Laboratory Data.*—Hematology, urinalysis, and serology were essentially normal.

*Radiographic Examination.*—Radiographic examination of the mandible showed a large, well-circumscribed, slightly loculated, radiolucent lesion involving the right mandible in the region of the angle, extending anteriorly to the first molar area, and involving practically the entire vertical ramus well into the coronoid process. The ramus appeared expanded, and there were several osteolytic areas along the alveolar ridge and the anterior border of the ascending ramus. The inferior posterior border showed solid bony continuity, and there was no evidence of pathologic fracture (Figs. 1 and 2).

A diagnosis of residual radicular cyst was made. It was thought that, since a radicular cyst is formed from a dental granuloma, this cyst might be a focus of infection.

*Tentative Diagnosis.*—Cyst of the mandible.

*Treatment and Course.*—The patient was admitted to the hospital on Dec. 21, 1955, and an operation was performed on Dec. 23, 1955. The usual preoperative medication was given. Following induction of intratracheal nitrous oxide–oxygen–ether anesthesia, an intraoral incision was made. This was extended from the coronoid process down the ramus and along the alveolar ridge of the mandible as far as the premolar teeth, with a vertical extension at the anterior end. The mucoperiosteum was detached by means of periosteal elevators when a thin cystic wall came into view. This cystic wall collapsed because of the escape of its yellowish contents. There was only one cavity, which was large with incomplete partitions.

Fig. 2.—Preoperative oblique view of the mandible on Nov. 6, 1955. Note osteolytic areas along the alveolar ridge and anterior border of the ascending ramus. There is no apparent pathologic fracture.

The cystic membrane was detached from the bony walls and was dissected free from the mandibular artery and nerve, which were preserved. The membrane could not be removed in one piece; in some places it was considerably thickened. The bony wall of the cyst was then inspected to determine that no membrane had been left. The mandibular nerve and vessel were found to traverse the cavity on the lingual side. On the posterior side a considerable amount of bone was found, while on the buccal and lingual sides the ramus was of parchmentlike character. The mucoperiosteal flaps were approximated and closed with interrupted 5-0 Dermalon sutures, and a small rubber drain was placed in the wound. The patient left the operating room in good condition and was taken to the recovery room.

On the first postoperative day the patient was comfortable, but there was a slight amount of oozing. The rubber drain was removed on the third postoperative day, and postoperative roentgenograms were made. On Dec. 28, 1955, the patient was given instructions for home care and was discharged, to be followed in the outpatient clinic.

*Postoperative X-ray Report (Dec. 27, 1955).*—Anteroposterior and oblique views of the mandible, taken as a progress follow-up subsequent to enucleation of the cystic membrane of the right mandible, showed no evidence of pathologic fracture (Figs. 3 and 4).

Fig. 3.—Postoperative roentgenograms made on Dec. 27, 1955.

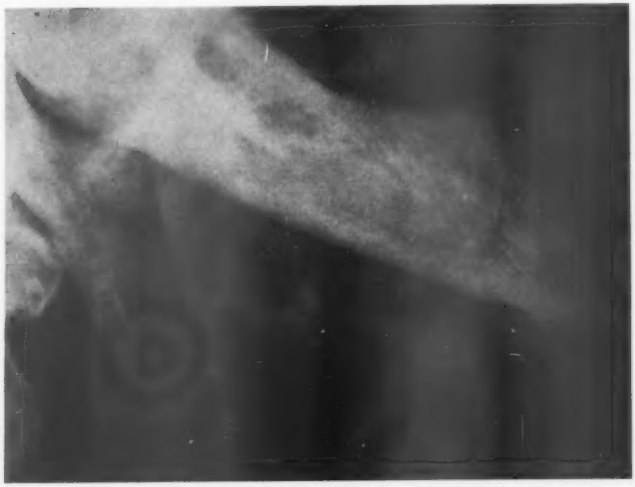


Fig. 4.—Postoperative oblique view of the mandible taken on Dec. 27, 1955.

*Histologic Findings.*—The first specimen consisted of a partially torn cyst measuring about 4 by 2 cm. The wall of the cyst was fairly smooth, with areas of roughening and hemorrhage (Fig. 5). The second specimen was another small piece of reddish pink cyst. Its wall was thin, averaging 1 mm. in thickness, and the lining was smooth. At one pole was attached a fragment of bone measuring 1.5 cm. The specimen was from the lingual side.

Microscopic examination showed the wall of a cyst consisting of an edematous, loose, connective tissue with many large oval nuclei. The surface was lined by a stratified epithelium consisting of several layers of oval, dark-staining nuclei. There was no definite

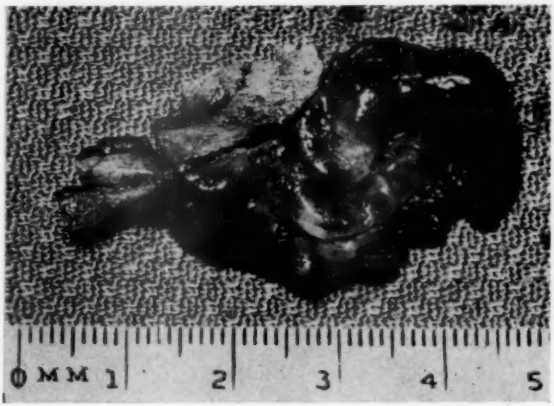



Fig. 5.—Gross specimen of a cyst. Note fragment of bone attached to one pole.

Fig. 6.—Final x-ray studies made on Dec. 3, 1957. Note filling-in of the bone defect.

basement membrane. Cell boundaries could not be distinguished. In another area there were collagenous bundles showing hyaline degeneration. There was infiltration by lymphocytes and plasma cells. Remnants of a stratified squamous epithelium could be seen.

*Diagnosis:* Residual cyst.

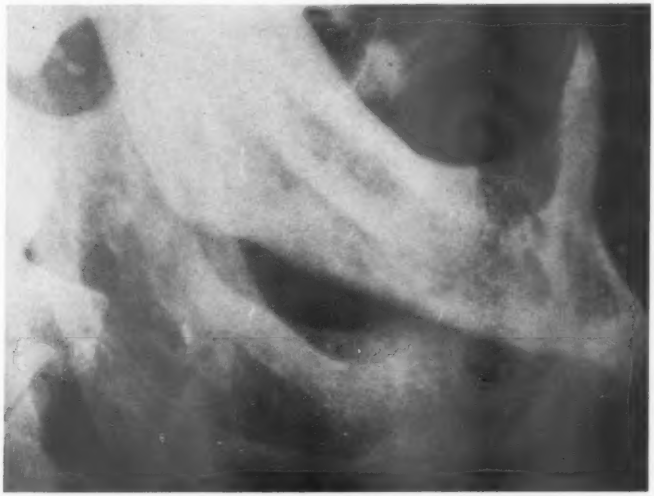


Fig. 7.—Postoperative oblique view of the mandible, on Dec. 3, 1957, showing complete bone regeneration on the operative site.

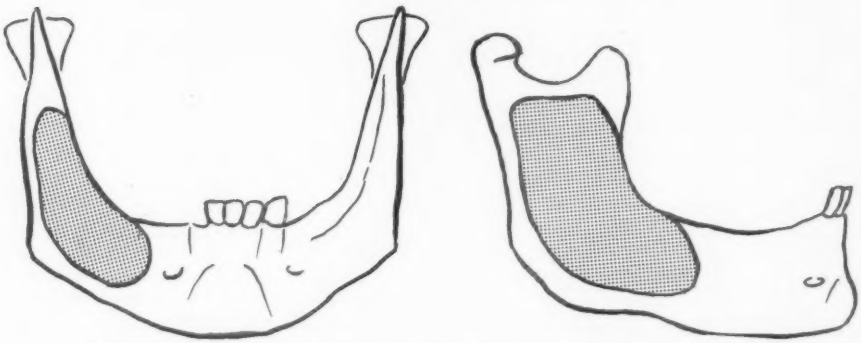


Fig. 8.—Diagrams illustrating a large odontogenic cyst of the mandible.

*Follow-up.*—The patient was seen periodically for checkup and was followed with roentgenographic examinations.

On June 25, 1956, roentgenograms revealed increased bone formation in the mandible, with no evidence of recurrence.

Final x-ray studies were made on Dec. 3, 1957, and progress views of the mandible in anteroposterior and both lateral projections showed complete bone regeneration on the operated site. There was no evidence of active infection or recurrence of the cyst (Figs. 6 and 7). This was compatible with a satisfactory postoperative course and was evaluated with the clinical findings and appraisal.

The clinical findings revealed a firm healing of tissue, with no evidence of recurrence, and the patient was discharged to the care of her local dentist.

## SUMMARY

A case involving a large odontogenic cyst of the mandible has been presented (Fig. 8). This was successfully treated by intraoral surgery through a conservative approach. The final result was filling-in of the bone defect.

# TETRACYCLINE WITH GLUCOSAMINE (COSA-TETRACYN) IN ORAL SURGERY

*George D. Dore, Jr., D.D.S., Seattle, Wash.*

ACCORDING to a recent survey, almost 75 per cent of the dentists who prescribe antibiotics for their patients select penicillin as their first choice to treat or prevent infections.[1] Yet, of the various antibiotics, penicillin is by no means the most effective, the safest, or the most convenient to use.

Oral infections usually are polymicrobic, caused by several varieties of gram-positive and gram-negative organisms. As compared with the more effective broad-spectrum antibiotics (Table I),[2] penicillin is seen to be one of the least effective agents for treating such infections. Some gram-positive organisms frequently isolated from root canals (notably *Streptococcus faecalis, Str. zymogenes,* and *Str. liquefaciens*) are resistant to penicillin.[3] Its efficacy against others has decreased considerably in recent years with the rapid development of resistant strains of organisms. Gram-negative organisms, which frequently are recovered from oral infections, are almost invariably resistant to penicillin.

So far as safety is concerned, the steady increase in the number of patients who are allergic to penicillin (now estimated at between 3 and 10 per cent of the population[4]) further decreases the value of penicillin therapy as it increases the risk. Finally, for full efficacy, penicillin cannot be administered orally, an obvious disadvantage and inconvenience in dental practice.

In view of the disadvantages of penicillin therapy, there is a pressing need to evaluate new antimicrobial agents as they become available to dentistry. The following evaluation was designed to determine the efficacy, safety, and convenience of a new oral preparation of tetracycline and to rate its value for use under clinical conditions encountered in the practice of exodontia and oral surgery.

As shown in Table I, tetracycline is a broad-spectrum antibiotic effective against both gram-positive and gram-negative organisms. In this evaluation, it was used with glucosamine as a potentiating agent.* Carlozzi,[5] Snell and Garkuscha,[6] and Welch and associates[7] report that glucosamine (2-amino-D-glucose), a common amino sugar which is a common constituent of human and animal studies, increases absorption of certain antibiotics from the gastrointestinal tract and potentiates the systemic concentration of tetracycline and its

*Cosa-Tetracyn, trademark of Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc., Brooklyn, New York.

congeners. Glucosamine itself is poorly absorbed, and up to 20 Gm. per day has been administered orally with no demonstrable toxicity.[8] The combination of glucosamine and antibiotics has been used successfully in medical practice,[9-11] but to date there are no reports on its use in oral surgery.

TABLE I. COMPARATIVE EFFICACY OF VARIOUS ANTIBIOTICS*

| ANTIBIOTIC | PERCENTAGE OF ORGANISMS SUSCEPTIBLE | |
|---|---|---|
| | GRAM-POSITIVE | GRAM-NEGATIVE |
| Penicillin | 59 | 2 |
| Tetracycline | 77 | 58 |
| Oxytetracycline | 73 | 51 |
| Erythromycin | 79 | 10 |
| Streptomycin | 48 | 47 |

*Adapted from Leming and Flanigan.[2]

METHOD

Antibiotic therapy with the tetracycline-glucosamine preparation (Cosa-Tetracyn) was administered to twenty-nine patients (fourteen men and fifteen women) who were selected at random from private practice of exodontia and oral surgery. Patients were between 15 and 70 years old, with an average age of 34 years.

Diagnoses included abscess, impaction, and periodontitis, among other disorders (Table II).

TABLE II. INDICATIONS FOR TETRACYCLINE THERAPY

| INDICATION | NUMBER OF PATIENTS |
|---|---|
| Impaction (third molar) | 11 |
| Abscess | 10 |
| Chronic periodontitis | 2 |
| Fracture of jaw | 2 |
| Osteitis | 2 |
| Pericoronitis | 1 |
| Cyst | 1 |

Each patient received capsules containing 250 mg. of tetracycline and 250 mg. of glucosamine. One capsule was administered three times daily to twenty-one patients, and one capsule was given every six hours to eight patients. The average duration of therapy was four days, with a range of from two to twelve days.

In addition to the antibiotic therapy, patients received appropriate oral surgery and concurrent therapy, when indicated, with sedative dressings, moist heat, saline rinses, etc.

RESULTS

The response to tetracycline with the potentiating factor, glucosamine, was excellent. The preparation was successful in office use in preventing infection and in reducing the need for frequent postoperative follow-up of patients. For

instance, in all cases of surgical removal of impacted third molars, prophylactic use of tetracycline with glucosamine promoted patient recovery and reduced postoperative visits to one-third the usual number for similar cases treated with penicillin.

Untoward effects were minimal. One patient developed a slight rash on his chest after two days of therapy. The rash disappeared within two days after therapy was stopped, and it may not have been a reaction to the antibiotic. There was no instance of nausea, vomiting, gastric upset, diarrhea, or flatus, as there often is with orally administered antibiotic therapy. One capsule three times daily proved adequate for prophylactic and anti-infection therapy.

## DISCUSSION AND CONCLUSIONS

The virtual absence of untoward reactions with the tetracycline preparation is particularly interesting in view of the stress which many investigators place on untoward effects when they refer to antibiotics other than penicillin. In this evaluation, the incidence of minor untoward effects of tetracycline was no higher than that expected with penicillin and, indeed, it may be lower. It is possible, of course, that the addition of glucosamine reduced the incidence of untoward effects by increasing absorption of the tetracycline from the gastrointestinal tract. As a result of improved absorption, less of the antibiotic may be left in the fecal stream to irritate the intestinal mucosa or disturb the intestinal flora.

The excellent responses to tetracycline, in this evaluation, emphasize (1) that antibiotics other than penicillin can be safe for use in dental practice and (2) that penicillin may no longer be the antibiotic of choice as compared to the newer antibacterial agents with broader spectra.

## SUMMARY

Although penicillin is by far the most frequently used antibiotic in dental practice, many other antibiotics have wider spectra of activity and are resisted by fewer strains of organisms. In this evaluation it was found that orally administered tetracycline, fortified with glucosamine to increase absorption of the antibiotic from the gastrointestinal tract, was remarkably effective in reducing and preventing infections associated with oral surgery and should be considered superior to penicillin for dental use.

## REFERENCES

1. Fouchard Academy Poll: Dentists Use Prescriptions Most in Treatment of Infection, Dental Survey 34: 480, 638, 1958.
2. Leming, B. H., and Flanigan, C., Jr.: Correlation of Sensitivity Patterns of Oleandomycin and Clinical Effectiveness, Sixth Annual Symposium on Antibiotics, Washington, D. C., October, 1958.
3. Grossman, L. I.: The Use of Disinfectants and Antibiotics in Endodontic Practice, J. Am. Dent. A. 53: 411, 1956.
4. Zimmerman, M. C.: Penicillinase Treatment of Fifty-two Patients With Allergic Reactions to Penicillin, in Welch, H., and Marti-Ibañez, F.: Antibiotics Annual, 1957-1958, New York, 1958, Medical Encyclopedia, Inc., pp. 312-320.
5. Carlozzi, M.: Evaluation of Antibiotic Blood Level Enhancement Factors, Antibiotic Med. 5: 146, 1958.

8. Snell, F., and Garkuscha, R.: Radioactive Oxytetracycline (Terramycin). III. Effect of Glucosamine Hydrochloride on Serum Concentrations, Proc. Soc. Exper. Biol. & Med. **98**: 148, 1958.
9. Welch, H., Wright, W. W., and Staffa, A. W.: The Effect of Glucosamine on the Absorption of Tetracycline and Oxytetracycline Administered Orally, Antibiotic Med. **5**: 52, 1958.
5. Marlow, A. A., and Bartlett, G. R.: Glucosamine and Leukemia, Proc. Soc. Exper. Biol. & Med. **84**: 41, 1953.
7. Cornbleet, T., Chesrow, E., and Barsky, S.: Use of Tetracycline With Glucosamine in Dermatology, Antibiotic Med. **5**: 328, 1958.
10. Nathan, L. A.: Use of Glucosamine-Potentiated Tetracycline in the Treatment of Upper Respiratory Infections in Children, Arch. Ped. **75**: 251, 1958.
11. Stone, M. L., Banford, J., and Bradley, W.: Treatment of Gynecological Infections With Glucosamine-Potentiated Tetracycline, Antibiotic Med. **5**: 322, 1958.

744 Stimson Bldg.

## ORAL MEDICINE

. . . . . .

### PRIMARY AMYLOIDOSIS OF THE TONGUE

**Report of a Case**

*Richard E. McCray, Jr., D.D.S., Harrisburg, Pa.*

A WHITE man, aged 70 years, reported to the Harrisburg Hospital in July, 1957, complaining of a swollen tongue.

*Chief Complaint.*—The patient complained (1) of having lost his voice, (2) of difficulty in eating, and (3) of swelling of the feet, legs, face, and eyes.

*Radiographic Examination.*—Three mandibular incisors showed evidence of extreme resorption. There were congestive changes in the lung fields secondary to cardiac insufficiency, complicated by a bilateral pleural effusion. Hypertrophic degeneration had produced changes in the cervical spine. There was a soft-tissue enlargement of undetermined cause in the left submaxillary area.

An electrocardiogram showed definite myocardial disease with first-degree A-V block and rather striking low voltage, suggestive of myxedema or pericardial effusion.

*Physical Examination.*—The patient, a slender 70-year-old man, was lucid and cooperative. He presented a swollen tongue, hoarseness, dyspnea, and loss of weight. His skin was warm, and he had no rashes. Two small nodes could be palpated under the left axilla; these were not tender. The conjunctivae were muddy; the pupils were round and equal and reacted to light accommodation; the extraocular muscles were normal. Numerous ruptured vessels were seen about the eyes (Figs. 1 and 2). The tongue was enlarged and smooth, with indentations from the teeth. There were three carious loose teeth (Fig. 3). The lips were irritated, and the gingivae about the teeth were inflamed. The trachea showed slight deviation to the right. The heart was normal, but expansion of the lungs was poor. There was a plus 3 pitting edema of the upper thighs, as well as some presacral edema. The hands showed arthritic changes.

From Harrisburg Hospital, Harrisburg, Pennsylvania.

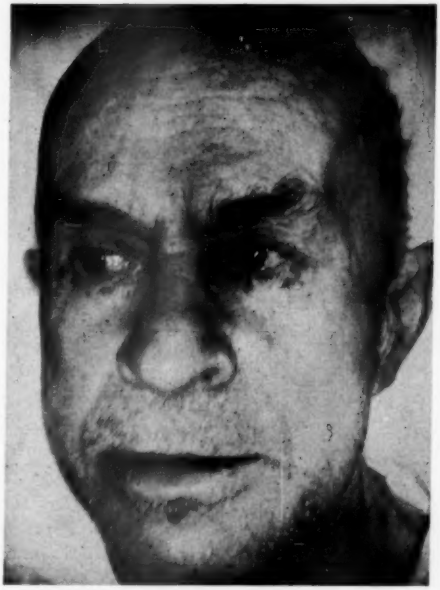


Fig. 1.

Fig. 2

Figs. 1 and 2.—Photographs showing numerous ruptured vessels about the eye. Note also muddy conjunctivae.

Laboratory findings were as follows:

*Urinalysis:*

Acid 5
Glucose, negative
Acetone, negative

*Blood Chemistry:*

Total protein 5.46
Globulin 1.60
Cholesterol 146
Urea 18 mg. per cent
Albumin 3.86
A. G. ratio 2.4
Blood sugar 90 mg. per cent

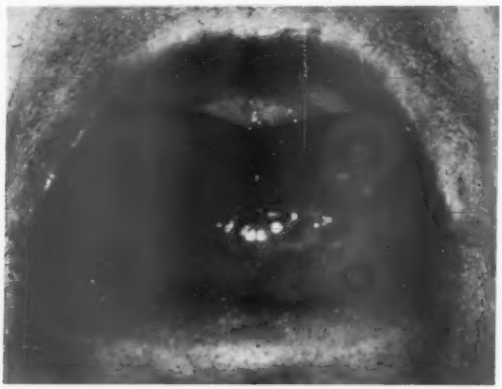


Fig. 3.—Note enlargement and smoothness of tongue.

*Hematology:*

Platelets 170,000
Bleeding time 1 minute 15 seconds
Clotting (venous glass) 7 minutes 3 seconds
(silicone) 22 seconds
Prothrombin time 85 per cent
Hematocrit 49
Hemoglobin 15.57
Sedimentation rate 30, corrected 20 mm. per hour.

*Biopsy.*—Under local anesthesia, a V-shaped wedge was removed from the side of the tongue. The wound was sutured and the specimen was sent for microscopic examination. The biopsy report indicated a hyaline-like intercellular matrix compatible with amyloid. This was confirmed by special staining (Figs. 4, 5, and 6).

Fig. 4.

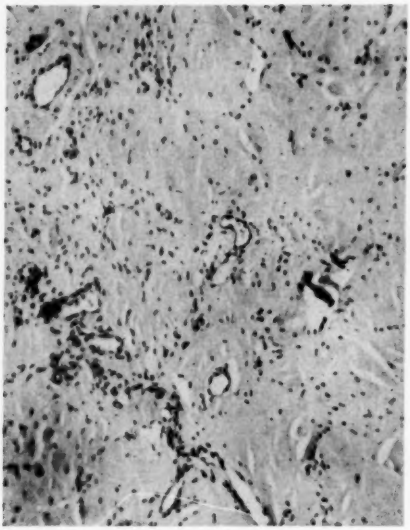


Fig. 5.

Fig. 4.—Low-power view of biopsy specimen from tongue.
Fig. 5.—Higher magnification of same specimen from tongue.

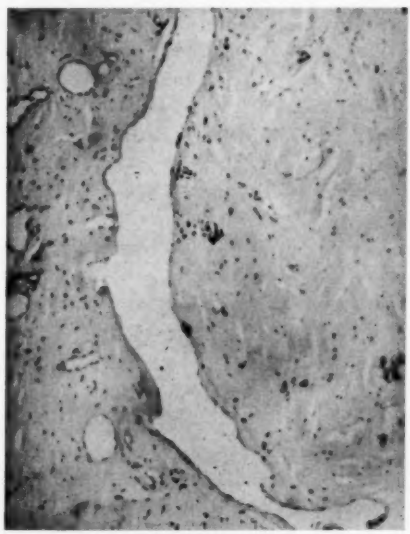


Fig. 6.—Still higher magnification of biopsy specimen from tongue.

*Diagnosis:* Primary amyloidosis.

*Postoperative Course.*—After corrective diet control and bed rest, the patient's condition was greatly improved. Proper medication was prescribed by his physician, and the patient was discharged from the hospital on Sept. 28, 1957. He died at home on Nov. 3, 1958.

*Autopsy.*—Autopsy findings confirmed the previous diagnosis. The cause of death was invasion of heart muscle by amyloid tissue.

## PHARMACOLOGY AND THERAPEUTICS

. . . . . .

# ILOSONE, THE PROPIONYL ESTER OF ERYTHROMYCIN

*Ronald S. Ping, D.D.S.,* and Estell E. Morris, D.D.S.,** Indianapolis, Ind.*

### INTRODUCTION

For many years penicillin has been considered the antibiotic of choice in the treatment of infections of dental etiology. However, two factors suggest the importance of a search for other anti-infective agents in dentistry. One is the increasing number of cases of anaphylactic shock, many of them fatal, due to penicillin administered parenterally.[1-3] The other is the evidence of an increasing incidence of penicillin-resistant organisms. The oral administration of penicillin largely overcomes the first difficulty. It does not affect the second.

Published reports on erythromycin[4-9] and phenoxymethyl penicillin[10-11] administered by mouth suggested these drugs as appropriate for study. Serious reactions to erythromycin have not been reported, and minor ones are uncommon.[12] Erythromycin is produced from a strain of *Streptomyces erythreus.* It was first isolated in 1952 by McGuire and his associates.[4] The propionyl ester, which produces faster, higher, and more enduring blood levels, was developed by Stephens.[13] Both erythromycin and its propionyl ester are bacteriostatic and bacteriocidal, depending upon the concentration of the drug. Spectacular results have been reported in the treatment of severe infections on the face and neck.[14]

Phenoxymethyl penicillin (also known as penicillin V) produces quicker and higher blood levels when given by mouth than does penicillin G. The potassium salt of penicillin V has these properties in even greater degree than the free acid; therapeutic serum levels are achieved in fifteen minutes, and peak levels are reached in thirty minutes.[15-17]

The bacterial flora commonly involved in dental infections include the streptococci, the staphylococci, the Friedländer bacillus *(Klebsiella pneumoniae),* and the organisms of Vincent *(Fusobacterium plauti-vincenti* and *Borrelia vincentii*). The spectra of penicillin, phenoxymethyl penicillin, erythromycin, and

*Associate Professor and Acting Chairman of the Department of Oral Surgery, Indiana University School of Dentistry.

**Instructor in Oral Surgery, Indiana University School of Dentistry.

the propionyl ester of erythromycin include these organisms. It is also worth noting that these antibiotics have no significant effect on the normal gram-negative flora of the intestinal tract. They therefore do not predispose to gastrointestinal infection with staphylococci or monilia.

## CLINICAL PROCEDURE

The therapeutic value of the antibiotics was tested in the treatment of 1,255 patients. The study extended over a period of twenty-four months and involved the administration of 18,215 doses of antibiotic. Patients of both sexes and a wide variety of ages were included. Prospective patients for the study were questioned for a history of allergy to antibiotics, and those with a positive history related to the agents to be studied were not included.

Nine hundred ninety-four of the patients were treated for acute dental infections, and 261 other patients were given antibiotics for prophylactic reasons because of a history of diabetes mellitus, renal disease, or other systemic disease in which postoperative dental infection would pose a special hazard. Patients were questioned routinely regarding difficulties experienced during the period of treatment.

Not all of the antibiotics were dispensed in identical capsules. However, they were supplied to the investigators in sealed, opaque envelopes labeled only in code, one envelope for each patient. In almost all instances the patients were questioned about results by a person other than the one who dispensed the envelope. Thus, the clinicians were ignorant of the identity of the antibiotic in each case. The code was not broken until the study was finished and the results had been summarized.

## RESULTS

The same criteria of effectiveness were applied to all the antibiotics studied. The results were judged to be good if subjective and objective improvement was noted within twenty-four hours; they were judged not good if the acute symptoms and signs extended beyond the first twenty-four hours without improvement. The results are presented in Table I. It will be noted that the

TABLE I. RESULTS OF THE STUDY

| ANTIBIOTIC | NO. OF PATIENTS | GOOD | NOT GOOD | PER CENT "GOOD" |
|---|---|---|---|---|
| V-Cillin,* 125 mg. | 82 | 61 | 21 | 74.38 |
| V-Cillin, 250 mg. | 520 | 417 | 103 | 80.19 |
| V-Cillin K,* 250 mg. | 131 | 112 | 19 | 85.65 |
| Ilotycin,* | 138 | 67 | 71 | 48.55 |
| Ilosone,* | 123 | 114 | 9 | 92.76 |
| | 994 | 771 | 223† | 77.56 |

*V-Cillin, penicillin V, Lilly.
V-Cillin K, penicillin V potassium, Lilly.
Ilotycin, erythromycin, Lilly.
Ilosone, propionyl erythromycin ester, Lilly.

†Two of these were placed on vancomycin with excellent results (both patients were hospitalized).

propionyl ester of erythromycin produced the highest percentage of good results—more than 92 per cent. Four per cent had poor results, and the results in 3 per cent were questionable, making a total of slightly more than 7 per cent rated as not good. The 250 mg. dose of potassium phenoxymethyl penicillin was found to be next in efficacy with more than 85 per cent good results. The 250 mg. dosage of the acid form of phenoxymethyl penicillin was next with 80 per cent good results, and the 125 mg. dose of acid phenoxymethyl penicillin was fourth with 74 per cent. A chi-square analysis of the results indicated that the distribution found would occur by chance less than once in 1,000 such experiments.[18]

No postoperative difficulties were reported for any of the patients who were treated prophylactically. Side effects for the entire study (18,215 doses) are shown in Table II. This incidence is so small that the percentage figures

TABLE II. SIDE EFFECTS WITH THE VARIOUS ANTIBIOTICS

| ANTIBIOTIC | NUMBER | PERCENTAGE INCIDENCE |
|---|---|---|
| V-Cillin, 125 mg. | 0 | 0 |
| V-Cillin, 250 mg. | 2 | 0.4 |
| V-Cillin K | 2 | 1.5 |
| Ilotycin | 3 | 2.2 |
| Ilosone | 0 | 0 |

and the differences in incidence do not have statistical significance. In order to be recorded, the side effects had to be of sufficient significance to require either discontinuation of the drug or counter therapy. Normally we discontinue a drug in the face of any complaint which might possibly be due to idiosynerasy or allergy. We consider this incidence of side effects extremely low. None of them were serious.

## SUMMARY AND CONCLUSION

A total of 1,255 patients were treated for acute dental infections or for prophylactic reasons. Four different antibiotic preparations were used to treat these patients.

The study indicated that the propionyl ester of erythromycin produced the highest percentage of good results. The usual adult dose administered was 250 mg. every six hours.

This drug could well be considered a first-choice antibiotic for dental patients. Its use would avoid the allergic reactions to penicillin, which have been occurring with increasing frequency,[12] and at the same time encourage dental use of an agent less likely to produce bacterial tolerance.

The authors wish to express their appreciation to the various members of Indiana University Faculties for their assistance and to Eli Lilly and Company for providing the drugs used in this study.

## REFERENCES

1. Lapin, J. H.: The Incidence of Allergic Reactions to Penicillin in Infants and Children, Ann. Allergy 13: 169, 1955.
2. Feinberg, S. M.: Allergy to Penicillin, J. A. M. A. 160: 778, 1956.

3. Cronk, G. A., and Naumann, E. E.: Oral Penicillin—Dosage, Toxicity and Clinical Application. In Welch, H., and Martí-Ibañez, F.: Antibiotics Annual 1954-1955, New York, 1955, Medical Encyclopedia, Inc., p. 111.
4. McGuire, J. M., Bunch, R. L., Anderson, R. C., Boaz, H. E., Flynn, E. H., Powell, H. M., and Smith, J. W.: Ilotycin, a New Antibiotic, Antibiotics & Chemother. **2**: 281, 1952.
5. Anderson, R. C., Harris, P. N., and Chen, K. K.: The Toxicity and Distribution of Ilotycin, J. Am. Pharm. A. **41**: 555, 1952.
6. Ping, R. S.: New Drugs in Dentistry, J. Indiana D. A. **35**: 9, 1956.
7. Heilman, F. R., Herrell, W. E., Wellman, W. E., and Geraci, J. E.: Laboratory and Clinical Observations on a New Antibiotic, Erythromycin (Ilotycin), Proc. Staff. Meet. Mayo Clin. **27**: 285, 1952.
8. Smith, J. W.: Dyke, R. W., and Griffith, R. S.: Absorption Following Oral Administration of Erythromycin, J. A. M. A. **151**: 805, 1953.
9. Griffith, R. S.: Blood Levels and Clinical Results With Erythromycin. In Welch, H., an Martí-Ibañez, F.: Antibiotics Annual 1954-1955, New York, 1955, Medical Encyclopedia, Inc., p. 269.
10. Brandl, E., Giovannini, M., and Margreiter, H.: Studies on the Acid Stable, Orally Efficacious Phenoxymethyl Penicillin (Penicillin V), Wien med. Wchnschr. **103**: 602, 1953.
11. Wright, W. W., and others: Serum Concentration and Urinary Excretion Following Oral Administration of Penicillin in Comparison With Penicillin G, Antibiotic Med. **9**: 490, 1955.
12. Herrell, W. E.: Hazards of Antibiotic Therapy, J. A. M. A. **168**: 1875, 1958.
13. Stephens, V. C.: Ester of Erythromycin. II. Derivatives of Cyclic Anhydrides. In Welch, H., and Martí-Ibañez, F.: Antibiotics Annual 1953-1954, New York, 1954, Medical Encyclopedia, Inc., p. 514.
14. Griffith, R. S.: Laboratory and Clinical Studies With Erythromycin Propionate. In Welch, H., and Martí-Ibañez, F.: Antibiotics Annual 1958-1959, New York, 1959, Medical Encyclopedia, Inc., p. 364.
15. Colquhoun, J., Scorer, E. C., Sandler, G., and Wilson, G. M.: Absorption of Free Acid, Potassium, and Benzathine Phenoxymethylpenicillin After Oral Administration, Brit. M. J. **1**: 1451, 1957.
16. Kaipainen, W. J., and Härkönen, P.: Serum Concentrations After Oral Administration of Phenoxymethylpenicillin Acid and Phenoxymethylpenicillin Potassium, Scandinav. J. Clin. & Lab. Invest. **8**: 18, 1956.
17. Peck, F. B., Jr., and Griffith, R. S.: Comparative Clinical Laboratory Studies of Potassium Penicillin V With Acid Penicillin V. In Welch, H., and Martí-Ibañez, F.: Antibiotics Annual 1957-1958, New York, 1958, Medical Encyclopedia, Inc., p. 1004.
18. Gruber, C. M., Jr., and Chernish, S. M.: Personal Communication.

# ENDOTRACHEAL ANESTHESIA AND TRAUMA INCIDENT TO ENDOTRACHEAL INTUBATION

*Kasimer Kowalski, D.M.D., East Hartford, Conn.*

ENDOTRACHEAL anesthesia is an accepted technique in the field of anesthesiology. Although the procedure was somewhat dubious in its juvenile stage, its further development was motivated by the need for better anesthesia during head and neck surgery and for controlled respiration during thoracic surgery. With the introduction of the laryngoscope by Chevalier Jackson, endotracheal anesthesia was no longer considered a "hit-or-miss" procedure; it could now be employed with accuracy. That this technique has gained considerable momentum is evidenced now by its daily use. Gratifying as this procedure may be, however, it may inadvertently predispose to local sequelae with possible serious complications. It is my aim in this paper to present some of the various complications, both direct and indirect, which one may encounter in using endotracheal anesthesia.

It may prove interesting to review briefly the historical development of endotracheal anesthesia. The word *endotracheal* is of Greek origin, *endo*—meaning "inside" and *tracheal* coming from the Greek *trachys,* meaning "rough." (The trachea is so named because the Greeks referred to it as the "rough vessel.") Endotracheal anesthesia had its first counterpart back in 1880, when William MacEwen inserted a metal tube into the trachea and administered chloroform for the removal of a tumor on the base of the tongue. With the motivation of developing a better technique for head and neck surgery, it was not until 1900 that the first period of development was noted. The period was influenced chiefly by the work of Franz Kuhm, who introduced a tube of coiled flat metal into the trachea with an "introducer" and then packed the pharynx with gauze soaked in oil.

The second period of endotracheal anesthesia stemmed from the so-called insufflation anesthesia and was motivated by the need for an expanded lung for surgical pneumothorax. Meltzer and Aver, in 1909, inserted a catheter into the larynx as far as the bifurcation of the trachea and proved that the lungs could be expanded when the chest was opened. Physiologic exchange of gases was lacking, however, and this technique left much to be desired.

The third period is due chiefly to the work of Magill and Rowbotham, two British anesthetists during World War I. Using a semiclosed technique, they inserted a wide-bore rubber tube into the trachea by which the patient could inhale and exhale.

Up to this point, all intubations were done by the touch-and-feel technique. With the introduction of the laryngoscope however, intubation could be performed under direct visualization. This brought a fourth period.

With the advent of Pentothal sodium and short-acting curare, endotracheal anesthesia finally reached the peak of high esteem. Endotracheal anesthesia has come a long way, but certain desirable features are still lacking. In the course of time, no doubt, these will be taken care of.

Experience and the literature indicate that the injudicious handling of the armamentarium of endotracheal anesthesia is probably responsible for the majority of sequelae. With proper respect given each piece of equipment, however, the incidence of trauma may be greatly reduced.

To begin with, a standard setup of equipment for endotracheal anesthesia consists of the following: laryngoscope, pharyngeal pack, connectors, endotracheal tubes, Magill forceps, suction catheters, bite block, adhesive tape, nasal airway tube, oral pharyngeal airway, a lubricant, nebulizer or throat sprayer, stylet, and curare.

In selecting the equipment, it is always wise to have more than one type of blade for the laryngoscope. The size of the endotracheal tube is very important, and it is a good practice to have several sizes ready just in case you find the larynx smaller than you anticipated. A pharyngeal pack should be wet, so that in its removal it will not adhere to the mucosal tissue and strip it. Where several types of anesthetic machines are used, the anesthetist should check the machine to be sure that he has the right connectors for the tubing before putting the patient under anesthesia.

The endotracheal tube has certainly earned its place as standard equipment for any person giving general anesthesia. It has come into widespread use as an effective means of establishing and ensuring a free airway. Intubation may be a lifesaving measure in the treatment of asphyxia, drug and gas poisoning, pulmonary edema, maxillofacial and head injury, cerebrovascular accident, acute edema of the glottis, and other conditions which may interfere with tidal exchange.

The endotracheal tube has a long and interesting history. It was used first as a means of artificial respiration in cases of drowning. In 1871, Trendelenburg first used it in man through a tracheotomy opening. Oral tracheal anesthesia was first used in 1880 by MacEwen, who employed an inhalation technique. The inhalation technique was almost abandoned until about 1926, when it again came into widespread use following the introduction of carbon dioxide absorption. The most probable cause of its improvement was the incentive to improve the airway under adverse conditions. Today, with the use of oropharyngeal packs and cuffed tubes, blood, vomitus, saliva, pus, and foreign bodies are excluded from the trachea. With the use of the closed system and carbon dioxide absorption, it is desirable to have a gas-tight fit

between the tube and the trachea. This permits the use of positive pressure without upsetting the even course of the anesthesia. Equally important is the fact that explosive gases are not allowed to wander about the operating room, where they might come in contact with some spark or cautery and become ignited.

Endotracheal intubation has been carried out in patients under many anesthetic drugs and combinations of drugs. These include deep inhalation anesthesia, with or without carbon dioxide, through cocainization of the nose, pharynx, and larynx, combined with light inhalation anesthesia and thiopental with cocainization and curare. Deep inhalation anesthesia is now seldom justified; its use merely to permit passing of an endotracheal tube is never justified. Second- or third-plane anesthesia induced and maintained in order to permit intubation and endotracheal anesthesia is often out of proportion to the duration and magnitude of the surgery performed. The postoperative morbidity from the anesthetic may be as great as that arising from the surgery or greater. With all due respect to the endotracheal tube, however, many papers have been written with regard to unusual sequelae during and after endotracheal intubation.

First, insertion of an endotracheal tube through the nostril may entail a certain amount of trauma, causing mucosal abrasions and lacerations, especially in the region of the turbinates and the anterior septum with resulting epistaxis. A condition that requires special consideration is that in which easy introduction of an endotracheal tube is prevented by distortion of the nasal, oral, or laryngeal passages by tumor or deformities due to previous surgery or trauma.

As for the laryngoscope, its insertion prior to intubation may entail a certain amount of trauma, depending largely on the experience of the anesthetist. Loosening or fracturing of teeth, necessitating extraction, is a complication which often is due to use of the upper incisors as a fulcrum. Laceration of the lip because the tissue has not been cleared from the blade, trauma to the gingiva, abrasions and lacerations of the hard and soft palate as well as the posterior wall of the pharynx, and edema of the pharynx as a result of pressing the blade against the posterior wall are also possible. The tongue is also in a position to be traumatized if it is caught between the blade and the teeth.

Among the complications reported, Shaw[1] presents a difficult intubation which took one hour between induction and intubation, resulting in edema of the larynx (which necessitated a low emergency tracheotomy). Donnelly, Grossman, and Grem[2] cited two unreported cases of laryngeal edema resulting after four-hour operations on children. Contact ulceration of the larynx after an operation lasting three hours and twenty-five minutes was reported by Fourior.[3] A very unusual accident was reported by Barnard.[4] While a naso-endotracheal tube was being passed by the blind technique, slight resistance was encountered; this was overcome and the tube was passed freely to the laryngeal region, where a slight resilient resistance was found. Examination with a laryngoscope disclosed that the tube was covered by the posterior pharyngeal mucosa. One commonly reported sequela of intubation is the formation

of a granuloma. Clausen[5] reported one at the posterior end of the larynx, growing on the right side. Tuft and Ratner[6] report two large, pedunculated granulomatous masses apparently attached to the vocal processes and almost completely occluding the posterior half of the larynx. A polypous granuloma after nasoendotracheal anesthesia with a history of "something moving up and down the throat" was reported by Cohen.[7]

Peimer and Feuerstein[8] reported that a review of the literature revealed twenty-one cases of granuloma of the larynx following endotracheal anesthesia. From a clinical standpoint, the most significant symptom of this condition was hoarseness occurring from one to two months after endotracheal anesthesia. Early diagnosis and prompt removal are of great importance. Reports by Smiley[9] and Kearney[10] of cases in which treatment was delayed from two to four weeks showed the patient developing apnea and marked dyspnea, and even reaching the point of impending asphyxia.

Lennon and Rovenstine[11] reported a very unusual accident in which rupture of an inflatable cuff led to a fatality. They could find no reports in the literature of other possible fatal sequelae due to rupture of the cuff. Adriani and Phillips,[12] however, in a recent publication state that this has been repeatedly cited by certain writers and their impression has been that this is a common and frequent accident. They go on to mention that the pathologic findings mentioned are strikingly similar to those ordinarily ascribed to blast injury resulting from explosions.

The presence of an abnormal epiglottis is of utmost importance. In a case reported by Pokrzywnicki,[13] an abnormal epiglottis occluded the entrance into the larynx during inspiration and on expiration was pushed out by air from the lungs, which almost proved fatal.

Trauma to the larynx is probably the most common sequela in endotracheal intubation. Consequently, this subject merits more consideration. Trauma to the larynx may be classified as "direct" and "indirect." The direct type of trauma is that occurring during the actual process of intubation by the anesthetist. This may occur in either the blind or the visual method of insertion of the endotracheal tube. Indirect trauma is that type of injury to the laryngeal mucosa which is caused either by static pressure of the tube in situ or by motion of the tube secondary to movement of the larynx and the tracheobronchial tree during respiration, coughing, straining, etc.

Donnelly, Grossman, and Grem[2] list six factors which influence damage to the larynx: (1) the degree of proficiency of the anesthesiologist in laryngoscopic procedures, (2) the individual anatomic characteristics of the patient which effect the ease of intubation (short neck, etc.), (3) the degree of relaxation and rapidity with which intubation must be effected, (4) the metal laryngoscope, (5) the diameter shape, and consistency of the endotracheal tube, and (6) duration of intubation.

"Gentleness is the essence of success." The skill and gentleness with which any intubation is performed profoundly influence the occurrence of sequelae

on the larynx. A command of the anatomy involved is indispensable, and experience in intubation is of prime importance. These two factors will greatly enhance the proficiency of the anesthesiologist.

Dwyer and colleagues[14] cite several factors that must be taken into consideration in using endotracheal tubes:

1. *Constitutional factors.* Changes in constitutional factors may lead to an easily traumatized respiratory passage. General debility from chronic illness, anemia, toxicity, vitamin deficiency, or alcoholism make for lower resistance and trauma. Dehydration leads to an increased friability of the epithelium of the respiratory tract and diminished secretions of mucus.

2. *Local factors.* Certain local abnormalities of the upper respiratory passage may predispose to trauma from the endotracheal tube. Structural anomalies of the larynx and trachea, displacement, compression, or contraction of the passage from infection, deformities, or tumors about the respiratory tract may cause undue pressure of the tube upon the mucosa.

3. *Movement.* Movement of the tube or of the tissues with which it is in contact is another factor leading to trauma. This motion is to-and-fro movement with respiration. Jackson[19] has described the following changes in the tracheobronchial tree during respiration: (a) elongation during inspiration, (b) shortening during expiration, (c) expansion during inspiration, and (d) collapse during expiration. During ordinary quiet respiration, linear movement may be slight but is greatly increased by hyperpnea, hypoxia, respiratory obstruction, or deep anesthesia. Movements due to coughing, swallowing, or hiccupping may become an important consideration in the treatment of coma, in resuscitation, or when the tube is left in place after operation.

4. *Shape of the tube.* The shape of the tube may be an important factor in the production of traumatic effects. The most commonly used tubes are curved in one plane (as the Magill). As the tube is passed along the floor of the nose, the tip strikes the posterior wall of the nasopharynx. The curve of the tube must increase sharply at this point. The inherent curve of the tube tends to bring the tip forward toward the larynx as it passes through the hypopharynx. Since the air column turns abruptly posteriorly at the level of the vocal cords, the tip will strike the anterior wall of the lower larynx or upper trachea just below the cords. The anterior curve of the tube must be reversed as it passes down the trachea, and this causes pressure against the anterior tracheal wall. The resilience of the tube will cause pressure at the posterior part of the larynx. The position of the head and shoulders is also important with regard to these pressure points. Raising and flexing the head will bring the upper pharynx forward and tend to lessen the curve that the tube must make at the larynx.

This will reduce the pressure at the posterior part and in the anterior trachea. Lowering and extending the head increases the angle at the vocal cords. Regardless of the position of the head, any resilient tube with an anterior curve passed by the nasal route will cause some degree of pressure at these points. The same principle applies when a curved tube is inserted by the oral route, but in this case the sharp curve at the nasopharynx is eliminated.

A few words about the prolonged use of an endotracheal tube are in order. There is no evidence that suggests a time limit during which a tube can be left in the trachea. Gillespie[15] has reported the use of an endotracheal tube left in for approximately fifty-one hours with no permanent damage. Foregger[16] cites a case in which an endotracheal tube was left in the trachea for 138½ hours and questions whether or not a human larynx may be intubated for long periods of time without damage to the larynx and vocal cords if they were not previously paralyzed by an injury. The patient himself was able to intubate his own trachea, according to the author, after he became accustomed to it.

This subject would not be complete without a discussion of cardiac arrhythmias, management of positve pressure, and tension pneumothorax and their relationship to endotracheal anesthesia.

Cardiac irregularities which develop during anesthesia are a matter of concern since they may precede serious or fatal cardiac disturbances. Arrhythmias which develop during anesthesia have been attributed to several factors. Among the vagal stimuli which are considered responsible for cardiac irregularities are those associated with instrumentation of the larynx and trachea. In a paper written by Jacoby and associates,[17] the effect of vagal stimulation and hypoxia on cardiac arrhythmias was discussed:

Vagal stimulation initiated by tracheal intubation may cause changes in electrocardiographic tracings. When the patient is well oxygenated, these changes are similar in nature and frequency of occurrence to those which follow induction of anesthesia and appear to be of little consequence. When blood oxygen saturation is markedly reduced (50 to 60%), pulse changes occur in almost all patients (91%) and the incidence of arrhythmia is four times as great as in well oxygenated patients. Arrhythmias occur in one out of every three poorly oxygenated patients, but only in one out of every ten well oxygenated patients. In the poorly oxygenated patient, the arrhythmias not only are more frequent but are more serious in nature. Patients frequently develop hypoxia when intubated by beginning students, even when the patient's lungs are first inflated with oxygen. In individuals with normal hemoglobin, the onset of slight cyanosis during intubation indicates hypoxia sufficiently great to require a pause for re-inflation of the lungs with oxygen. Anemic patients require more consideration since cyanosis would develop only after more severe hypoxia had occurred and anemic patients are less able to tolerate hypoxia, and the more serious are the cardiac responses to vagal stimulation.

The clearest understanding of positive pressure in endotracheal anesthesia may be obtained by focusing attention on the respired gases. These gases are confined to a system consisting of the lungs, bronchioles, and tracheobronchial tree of the patient and the tracheal tube, tubes, adapters, valves, $CO_2$ absorbers, and breathing bag of the machine. Within this system there is a back-and-forth movement of gases between the two end points of the system, namely, the lungs

and the breathing bag. When flowing through certain points of the connecting channels, the gases meet resistance, and transitory pressure changes develop. These pressure changes are transitory fluctuations around the existing mean pressure and depend on the particular part of the system where the pressure is measured. However, I will consider only the mean pressures in this presentation.

The arithmetic mean of the maximum and minimum readings is the mean systemic pressure. For example, when the maximum and minimum readings are 8 and 4 cm. of water during expiration and inspiration, respectively, the mean pressure is 6—the arithmetic mean of 8 and 4.

The mean systemic pressure depends on the relationship between the capacity of the system and the volume of gases present therein. If the volume of gases does not exceed the capacity of the system, the systemic pressure equals the atmospheric pressure. If the volume of gases is larger than the capacity, the gases will be under greater pressure than atmospheric pressure, and positive pressure will exist in the system. Positive pressure can be produced either by allowing an excess amount of a gas to flow into the system or by squeezing the breathing bag, thus reducing its capacity.

Intrathoracic or intrapleural pressure, which exists within the pleural cavities and mediastinum, is not identical with the systemic pressure. Usually it runs parallel with it but is about 5 to 6 cm. of water less. This difference in pressure corresponds to the force exerted by the elastic recoil of the lungs. Because of this difference, the intrathoracic pressure is negative under normal circumstances when the systemic pressure is atmospheric. This is significant because of its support to the circulation, that is, to the venous return to the heart. The filling of the large veins in the mediastinum and the right auricle is facilitated by the sucking effect of the intrathoracic negative pressure. If the systemic pressure is raised about 5 to 6 cm. of water, the intrathoracic pressure becomes positive. Whereas the negative intrathoracic pressure aids the circulation, positive intrathoracic pressure has an adverse effect; it obstructs the venous return to the heart, thereby reducing cardiac output. These circulatory changes are proportional to the extent and duration of the intrathoracic positive pressure, and they are of increased significance in patients whose circulation is already handicapped.

There is always the possibility of promoting mediastinal emphysema, with or without concomitant pneumothorax, in intubating. A review of the anatomy of the lower neck reveals that between the middle and deep layers of the deep cervical fascia in the area containing the trachea and the esophagus there is a direct communication between the neck structures and the superior mediastinum. It is obvious, therefore, that air passes into the mediastinum whenever perforation of the trachea takes place, involving division of the middle layer of the deep cervical fascia.

In concluding, something should be said about endotracheal extubation. It is generally agreed that extubation should be performed in light planes of anesthesia to reduce the time that the patient is without his protective laryngeal

and pharyngeal reflexes. These reflexes, however, can be detrimental to the patient at the time of extubation. Stimulus to the upper respiratory tract reflexes causes the following:

1. Laryngospasm—Hypoxia—Cardiac arrhythmias
   Cardiac arrest
2. Bucking—Increased cerebral spinal fluid pressure—Cerebral congestion
3. Jaw rigidity, inadequate toilet— Aspiration, nonvisualization of vocal cords— Postoperative pulmonary morbidity

The method that we employ at present, by which we insert a catheter into the endotracheal tube and remove the endotracheal tube with the catheter sucking any mucus, blood, or blood clots, is by far the most popular method. It would seem that with the insertion of the catheter, however, we aspirate not only blood, mucus, etc. but also air which is in the endotracheal tree. If the patient goes into spasm, this would seem likely to increase the severity of hypoxia.

Lambie[18] discussed the use of succinylcholine during endotracheal extubation and arrived at the following conclusion from his experiment. Thirty-six patients were studied, of whom twenty received succinylcholine and the remainder served as controls. All patients were studied with continuous oximetry and electrocardiography.

With the use of succinylcholine, the decrease in oxygen saturation during extubation is minimal. Without succinylcholine, the average fall in oxygen saturation is greater and there is a greater variation in the degree of hypoxia.

The pressor reflexes of extubation were found to be similar to those of intubation. No correlation was found between these reflexes and the decrease in oxygen saturation.

Electrocardiographic changes other than sinus tachycardia were found to be related to decreases in oxygen saturation of 10 per cent or more. All these cases occurred in the control series, and all the patients exhibited bucking. This study demonstrates objectively that short periods of subclinical hypoxia can be associated with transient electrocardiographic changes.

A thorough toilet of the supralaryngeal region can be performed under direct vision during the period of apnea. This prevents postoperative pulmonary complications due to the aspiration of foreign material, with the first inspiration following the removal of the tube. Finally, postoperative sore throat is minimized with this technique.

## CONCLUSION

Endotracheal anesthesia has been discussed with regard to its application. Trauma, often encountered in endotracheal intubation, was covered quite extensively. The subject matter in this article is by no means complete. However, an understanding of this material will facilitate a better and safer anesthesia, as well as promote greater respect for the agent and material used for its adminstration.

REFERENCES

1. Shaw, W. M.: Edema of the Larynx, Anesthesiology **7**: 416, 1946.
2. Donnelly, W. A., Grossman, A. A., and Grem, F. M.: Local Sequelae of Endotracheal Anesthesia, Anesthesiology **9**: 490, 1948.
3. Fourior, J. B.: Contact Ulcer of Larynx, Arch. Otolaryng. **36**: 238, 1942.
4. Barnard, J.: Unusual Accidents During Intubation, Anesthesiology **3**: 126, 1948.
5. Clausen, R. J.: Unusual Sequelae of Tracheal Intubation, Proc. Roy. Soc. Med. **25**: 1507, 1925.
6. Tuft, H. S., and Ratner, S. H.: Laryngeal Polypoid Granuloma Following Endotracheal Anesthesia, Ann. Otol., Rhin. & Laryng. **56**: 187, 1947.
7. Cohen, M.: Tumor of Vocal Cord Following Nasal Endotracheal Anesthesia, Brit. M. J. **1**: 283-284, 1938.
8. Peimer, R., and Feuerstein, S.: Laryngeal Granuloma Following Endotracheal Anesthesia, Laryngoscope **61**: 165, 1951.
9. Smiley, W. A.: Polypoid Granuloma of Larynx Following Endotracheal Anesthesia, Ann. Otol., Rhin. & Laryng. **49**: 556, 1940.
10. Kearney, H. L.: Bilateral Granuloma of Larynx Following Endotracheal Anesthesia, Ann. Otol., Rhin. & Laryng. **55**: 185, 1946.
11. Lennon, B. B., and Rovenstine, E. A.: Fatality Following Rupture of Inflatable Cuff on Endotracheal Airway, Anesth. & Analg. **18**: 217, 1939.
12. Adriani, J., and Phillips, M.: Use of the Endotracheal Cuff, Anesthesiology **18**: 1, 1957.
13. Pokrzywnicki, S.: Impaction of the Epiglottis During Anesthesia, Anesthesiology **8**: 47, 1953.
14. Dwyer, C., Krenenberg, S., and Saklad, M.: The Endotracheal Tube: A Consideration of Its Traumatic Effects With Suggestions for the Modification Thereof, Anesthesiology **10**: 714, 1949.
15. Gillespie, N. A.: Probing Use of an Endotracheal Tube: Report of a Case, Anesthesiology **3**: 127, 1942.
16. Foregger, R.: Use of Endotracheal Tube in Therapy of Post-traumatic Pulmonary Secretions, Anesthesiology **7**: 285, 1946.
17. Jacoby, J., Ziegler, C., Hamelberg, W., Magg, A., Klassen, K., and Flory, F.: Cardiac Arrhythmias: Effect of Vagal Stimulation and Hypoxia, Anesthesiology **16**: 1004, 1955.
18. Lambie, R. S.: The Use of Succinylcholine During Endotracheal Extubation, Anesthesiology **17**: 47, 1956.
19. Jackson, C.: New Mechanical Problem in the Bronchoscopic Extraction of Foreign Bodies From Lungs and Esophagus, Ann. Surg. **75**: 1, 1922.

ORAL ROENTGENOLOGY

*American Academy of Oral Roentgenology*

*Arthur H. Wuehrmann, Editor*

# A 65 OR A 90 KILOVOLT X-RAY MACHINE?

*Harry D. Spangenberg, Jr., D.D.S., M.S. in Dent. Surg.,* and*
*M. L. Pool, Ph.D.,** Columbus, Ohio*

## INTRODUCTION

THE answer to the question of whether a dentist should purchase a 65 kilovolt or a 90 kilovolt dental x-ray machine is not simple. The answer must involve some knowledge of the science of x-ray physics as it is related to the production of a roentgenogram of excellent diagnostic quality. One of the many factors contributing to roentgenographic quality is the kilovoltage used in the production of the x-ray radiations employed in the exposure technique. The criteria for judging the quality of a dental roentgenogram are likely to vary from dentist to dentist, inasmuch as quality is subjective in nature and thus is very difficult to define. It is possible to judge a roentgenogram objectively, however, by measuring the actual blackening of various areas which are exposed to x-ray radiations produced by predetermined kilovoltages. If the kilovoltage is altered, the resulting blackening of the various areas of the roentgenogram is also altered.

## HISTORICAL CONSIDERATIONS

Although x-ray radiations could possibly have been produced by Morgan[1] as early as 1785 and certainly by many other scientists (for example, Plücker

Presented at the scientific session of the centennial meeting of the American Dental Association on Sept. 17, 1959. The paper was released by the American Dental Association for publication under the auspices of the American Academy of Oral Roentgenology.

Part of the information presented in this paper was obtained under Research Contract AF 41(657)209 monitored by the School of Aviation Medicine, Air University Command, United States Air Force; part under Research Contract AF 18(600)1305 sponsored by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command; and part under Research Contract NR 105-185 sponsored by the Office of Naval Research, Department of the Navy.

*Associate Professor of Dentistry, College of Dentistry, The Ohio State University.

**Professor of Physics and Astronomy, College of Arts and Sciences, The Ohio State University.

in 1850, Geissler in 1860, Hittorf in 1869, and Lenard in 1892) who were investigating the passage of high-voltage electricity through gases held at partial pressure, it remained for Röntgen to discover their existence. In 1901 Wilhelm Conrad Röntgen was awarded the first Nobel Prize in physics for his discovery of a "new kind of rays" which was announced to the world in three publications—the first in December of 1895, the second in March of 1896, and the third in May of 1897. Shortly thereafter this new ray became known as the x-ray, and at a slightly later time it was called the roentgen ray.

The nature of the radiation was studied intensively by many investigators. Although the experimental studies of Haga and Wind[2] in 1899 strongly suggested the wave nature of the radiations, it was not until 1912 that von Laue, Friedrich, and Knipping[1, 2] positively confirmed that the x-ray radiations were waves belonging to the electromagnetic spectrum, the existence of certain properties of which had been foretold theoretically by Helmholtz in 1890.[1] The electromagnetic spectrum is a family or group of waves which, according to the classic wave theory, are rhythmic electric and magnetic oscillations.[3] These waves have one property in common. They move with the same velocity, namely, 186,000 miles per second or 3 by $10^{10}$ cm. per second. They differ from one another in their wave lengths. Different wave lengths produce different physical and biologic responses. The longest waves in the spectrum have a length of $10^{11}$ cm., and the shortest have a length of $10^{-12}$ cm.

It is convenient to place the waves of various lengths in groups or regions according to the response which they produce. The longest waves are placed in the induction-heating group. Radio waves and alternating current belong to this group. The next region, composed of shorter waves, is the infrared region. This group is followed, in descending order of length, by the visual-light region, the ultraviolet-light region, the x-ray and gamma-ray region, and the cosmic-ray region.

Historically, the x-ray and gamma-ray region was considered to be two separate regions, the x-ray region being composed of longer waves than the gamma-ray region. Today, because of technological developments, it is possible to produce x-ray waves which are just as short as or are shorter than the shortest known gamma rays.[4-6] Furthermore, there are many gamma rays which are longer than many of the x-ray waves produced by clinical dental x-ray machines.[7-9] X-rays and gamma rays may be differentiated only in the manner in which they are produced. In general, it may be said that x-ray waves result from phenomena involving electrons whereas gamma rays result from phenomena involving the nucleus of an atom.

## THE DENTAL X-RAY MACHINE

The dental x-ray machine as we know it today has evolved from machines which, judged by today's standards, were crude indeed.[10] The tube with which Röntgen discovered the x-ray was gas filled. Those tubes were temperamental, and the technical precision which is considered essential today was only a dream

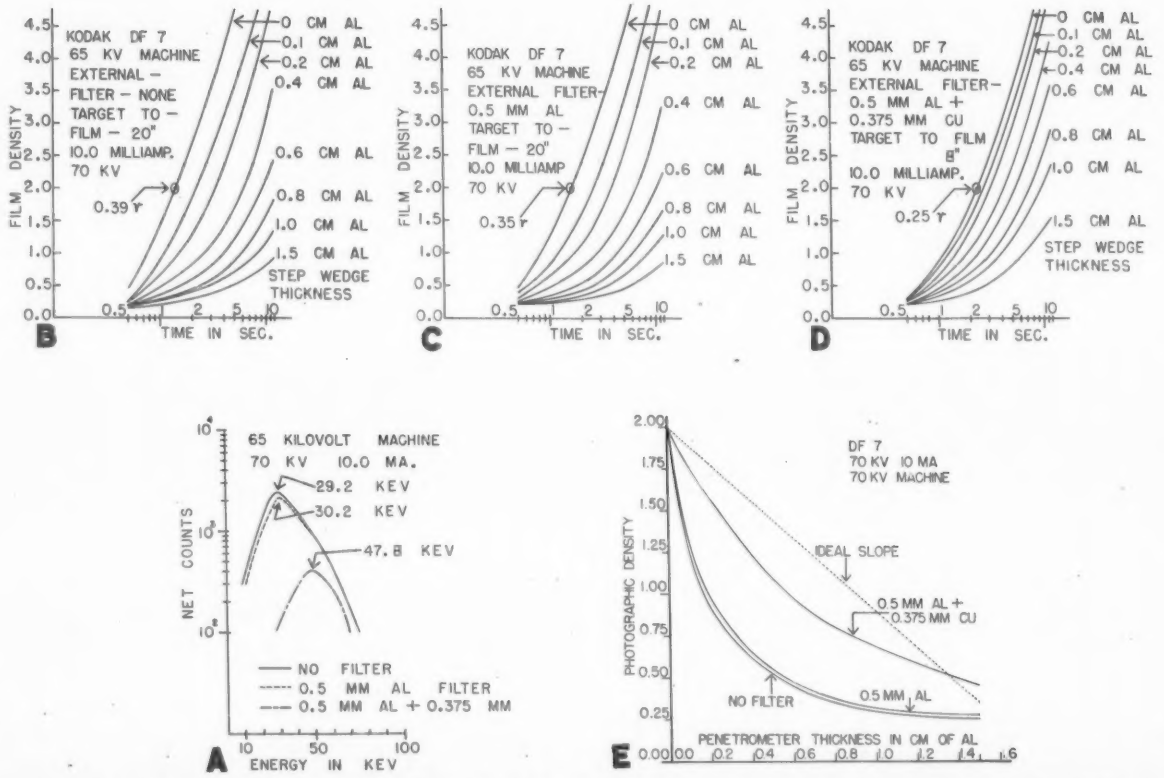



Fig. 1.—*A*, The spectrum of a 65 kv. dental x-ray machine operated at 70 kv. with no external filter, with 0.5 mm. of aluminum external filter, and with 0.375 mm. of copper and 0.5 mm. of aluminum external filter, as measured by a scintillation spectrometer. *B*, *C*, and *D*, Roentgenographic densities under various aluminum step-wedge thicknesses, produced by a series of exposure times and plotted as Hurter-Driffield curves. *E*, Density versus step-wedge aluminum penetrometer thickness.

then. One of the important advances in the development of the dental x-ray machine was the introduction of the Coolidge tube in 1913.[11] Along with the Coolidge tube, the discovery of alternating current by Westinghouse and the advances in the method of high-voltage production by the use of transformers have made possible the precision instrument available to us today.

*The Spectra of Radiations Emitted by a 65 Kv. Dental X-ray Machine, Without and With External Filtration.*—When the electrons produced by the filament of the x-ray tube are attracted by the high voltage to the target, a collision occurs. This results in the production of heat and x-rays, both of which are very important to the dentist. Prolonged exposures can cause the production of so much heat that the equipment may be damaged. Each manufacturer makes certain recommendations regarding the technique of operation, and these should be followed carefully. The x-rays that are produced are a mixture of waves of many different lengths.

The measurement of the relative intensity of the mixture of waves was formerly time consuming.[12] Within recent years new methods have been introduced,[13] so that now the spectrum of a dental x-ray machine operated under clinical conditions may be measured in a short time.[14] The length of the shortest wave produced by the x-ray machine is related mathematically to the highest voltage applied. Thus, the length of the shortest wave produced by a 65 kv. dental x-ray machine within the range of normal operation is considerably longer than the shortest wave produced by a 90 kv. dental x-ray machine. Fig. 1, *A* illustrates the distribution of the various wave lengths produced by a 65 kv. x-ray machine operated at 70 kv. and 10 Ma., conditions under which the dentist frequently operates his x-ray equipment when exposing a dental x-ray film for the production of a diagnostic roentgenogram. In Fig. 1, *A*, it may be seen that the intensity of the short waves is relatively small when compared with the region in which the intensity is greatest. Although the length of the wave may be described in Angström units, which are very small units of linear measure, it is more convenient to designate the length of the wave in terms of its energy in kiloelectron volts (Kev.). This is to be differentiated from the kilovoltage, which is the electrical potential applied to the tube of the x-ray machine during its operation.

If the x-ray beam produced when the 65 kv. x-ray machine is operated at 70 kv. is subjected to external filtration by 0.5 mm. of pure aluminum, some of the low-energy x-rays are eliminated by the amount shown in Fig. 1, *A*. If the beam is filtered by 0.375 mm. of copper and 0.5 mm. of aluminum, as suggested by Yale and Goodman,[15] the x-rays of lower intensity are eliminated by an even greater amount, as shown in Fig. 1, *A*. Critical examination by visual inspection of roentgenograms produced by an x-ray beam emitted from a 65 kv. machine operated at 70 kv., which is subjected to no external filtration or to 0.5 mm. of aluminum filtration, reveals no easily describable differences. However, when this x-ray beam is filtered by 0.375 mm. of copper and 0.5 mm. of aluminum acting as a single filter, the resulting roentgenograms do have a color which

is distinctly different. The differences seen in the roentgenograms of the same subject but produced under different filtration conditions are more easily described by objective than by subjective means.

*Hurter-Driffield Curves, Density Step-wedge Curves, and Roentgenographic Quality (a Study Using a 65 Kv. Dental X-ray Machine).*—The foundations for this type of investigation were laid by Hurter and Driffield in 1890.[16, 17] Although their studies were carried out with visible light, it has been found that the same principles obtain with only slight modification if x-ray radiation is substituted for light.[18]

This technique of the application of sensitometry as a method of research in dentistry was extensively studied by Hodge and associates.[19] If an aluminum step-wedge penetrometer is substituted for a patient, and if a series of exposures is made at various increments of time, roentgenograms of the penetrometer will be obtained following processing procedures. Those roentgenograms exposed for a short period of time will be less black than those exposed for a longer period of time. The exact amount of blackening of the various parts of the roentgenogram may be measured by an instrument called a densitometer. If the blackening measured in units of density of the various areas of each of the roentgenograms is plotted against the logarithmic value of the various exposure times, a graph will be produced which has the characteristics shown in Fig. 1, *B* and *C*. These graphs differ from one another only slightly, in spite of the fact that the x-ray radiations used for exposure were unfiltered in Fig. 1, *B* and filtered with 0.5 mm. of aluminum in Fig. 1, *C*. The x-ray radiations used for exposures in Fig. 1, *D*, however, were filtered with 0.375 mm. of copper and 0.5 mm. of aluminum. It will be noted that the characteristics of the curves have been altered when they are compared with those shown in Fig. 1, *B* and *C*.

A roentgenogram with a background density in the neighborhood of 2 will be pleasing to most practicing dentists if the roentgenogram is viewed by means of a conventional view box. For this density, approximately 0.39 r unit was required when the x-ray beam was unfiltered, 0.35 r when the beam was filtered with 0.5 mm. of aluminum, and 0.25 r unit when the beam was filtered with 0.375 mm. of copper and 0.5 mm. of aluminum. If the blackening under the various thicknesses of the aluminum step-wedge penetrometer is plotted for the exposure time which produces a density of 2 on that part of the roentgenogram not covered by the penetrometer, curves are produced for the various filter configurations already discussed. Such a series of curves is illustrated in Fig. 1, *E*. These curves are of great clinical importance, for they graphically represent the information available to the dentist under the conditions of exposure used in the production of a clinical roentgenogram. It is interesting to note that there is but slight difference in densities when the blackening under the 1.5 cm. step of the aluminum penetrometer is compared with that under the 1.0 cm. step of the aluminum penetrometer when no filter or 0.5 mm. of aluminum filter is placed in the x-ray beam. Clinically, this means that when these exposure techniques are used, the diagnosis of a carious lesion would be practically impossible

if the carious lesion was small. It is also clinically important that in spite of the fact that in one case the x-ray beam is filtered and no filter is used in the other, fewer r units are required to produce practically the same results.

An ideal roentgenogram for viewing by conventional light intensities should have a density range of from 2 to 0.35.[17] Graphically presented, this would be represented by the dotted line in Fig. 1, *E*. It is interesting to note that when the x-ray beam is filtered with copper and aluminum, as described above, the curve most nearly approximates that of the ideal condition represented by this line.

*The Spectra of Radiations Emitted by a 90 Kv. Dental X-ray Machine, With and Without External Filtration.*—The radiations emitted by a 90 kv. dental x-ray machine were subjected to the various filter configurations mentioned above. The relative intensities of the x-ray energies are illustrated in Fig. 2, *A*. There is but slight alteration in the spectral distribution when the beam is unfiltered or filtered with 0.5 mm. of aluminum. However, there is a marked shift in the region of the peak energy as well as in the intensities of the lower energies when copper and aluminum are used as a filter.

*Hurter-Driffield Curves, Density Step-wedge Curves, and Roentgenographic Quality (a Study Using a 90 Kv. Dental X-ray Machine).*—Fig. 2, *B*, *C*, and *D* show curves plotted from data obtained in the same way as when the effect of the radiations from a 65 kv. machine was investigated. The same type of x-ray film was used. These curves have certain similarities and also certain differences. In general, it may be observed that the slopes produced by the blackening of the areas of the roentgenograms under the various penetrometer steps are separated by a more even spacing than they were when radiations from a 65 kv. machine were used.

The curves in Fig. 2, *E* are obtained by treating the data in the same way as in Fig. 1, *E*. There is marked similarity in the over-all pattern. It differs, however, in that the density of the film under the 1.5 cm. aluminum penetrometer step is further above the ideal slope, represented by the dash line, when the 90 kv. copper-and-aluminum-filtered beam is used instead of the 70 kv. copper-and-aluminum-filtered beam. Furthermore, the densities under the 0.1 to 1.0 cm. aluminum penetrometer steps are closer to the ideal slope when radiations, filtered by copper and aluminum from the 90 kv. machine are used in place of similarly filtered radiations from a 65 kv. machine.

From a clinical point of view, the dentist must decide what he most wishes to visualize. He must decide which type of roentgenogram is best suited for the diagnostic problem at hand. Again, as in the case of the 65 kv. x-ray machine, the dosage required to produce a satisfactory roentgenogram when the 90 kv. machine is used is considerably lessened by the introduction of filters in the x-ray beam.

## RADIOACTIVE ISOTOPES AS A SOURCE OF RADIATIONS, A FUTURE POSSIBILITY

In 1947 a skull roentgenogram of excellent quality was made by means of radiations from cesium$^{131}$. A reproduction of this roentgenogram was published

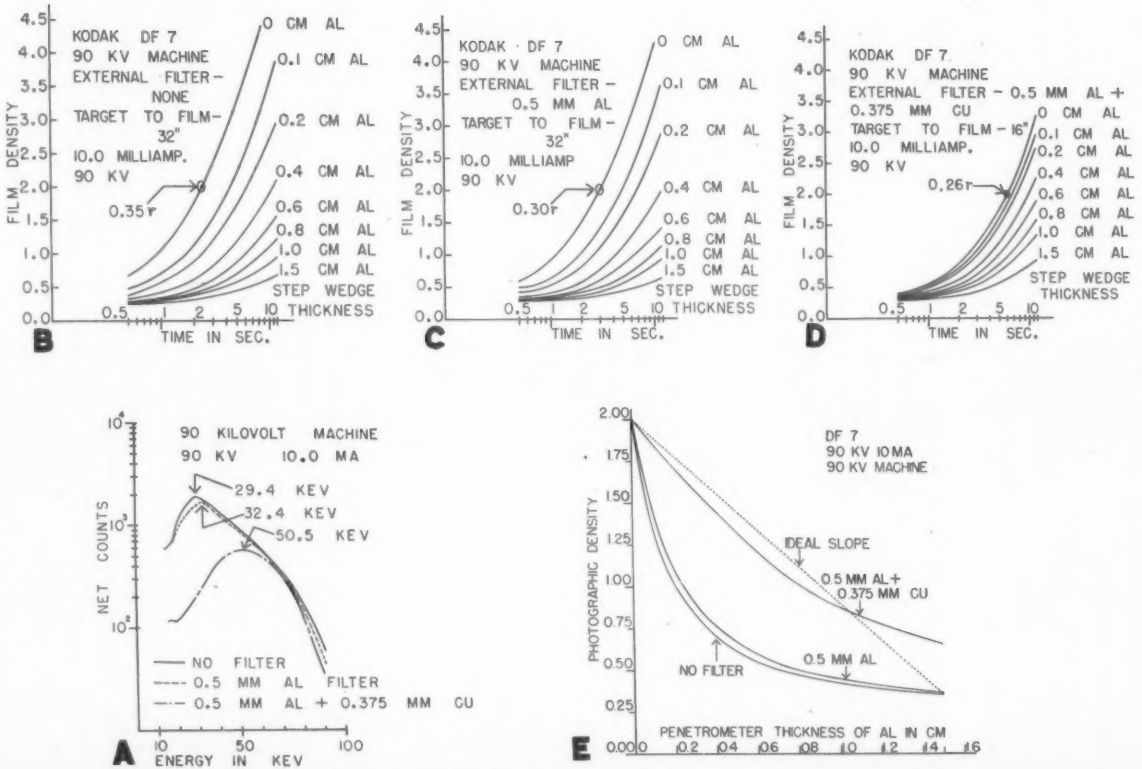



**Fig. 2.**—*A*, The spectrum of a 90 kv. dental x-ray machine operated at 90 kv. with no external filter, with 0.5 mm. of aluminum external filter, and with 0.375 mm. of copper and 0.5 mm. of aluminum external filter, as measured by a scintillation spectrometer. *B*, *C*, and *D*, Same as Fig. 1, *B*, *C*, and *D*. *E*, Density versus step-wedge aluminum penetrometer thickness.

in 1948.[8] The radiation from cesium[131] is unlike radiations from the conventional x-ray machines in that only a single energy is emitted rather than a mixture of energies, as in the case of the x-ray machines. This isotope has a very short half-life and probably will not be of great importance as a radiation source in the field of isotopic radiography.

A reproduction of a roentgenogram produced with radiations from cerium[144]-praseodymium[144] was published in 1958.[9] A spectral analysis of the energies emitted by this isotope is shown in Fig. 3, *A*. It will be noted that some very high-energy gamma rays are emitted, which makes shielding a real problem. In spite of the high energy of some of the radiations, good radiographs are produced. The thin ascending ramus of the mandible is visualized, as well as the petrous portion of the temporal bone. A Hurter-Driffield curve is shown in Fig. 3, *B*. Radiations which will visualize a variety of tooth sizes and bone densities on a single radiograph characteristically produce Hurter-Driffield curves of this shape.

A radiographic reproduction produced by radiations from samarium[145] was published in 1958.[9] Hurter-Driffield curves derived from radiographs exposed for various increments of time to radiations from this radioactive isotope are shown in Fig. 3, *D*. The characteristics of this series of curves are similar to those shown previously which were derived from data obtained from films exposed to x-ray radiations from an x-ray machine. An analysis of the radiations from samarium is shown in Fig. 3, *C*.

A radiograph produced by radiations from hafnium[175] has been made in our laboratory. The spectral analysis of the radiations produced by hafnium[175] is shown in Fig. 3, *E*. Fig. 3, *F* shows the distribution of the Hurter-Driffield curves. A marked similarity exists between this set of curves and those produced with radiations from cerium-praseodymium[144].

A roentgenogram produced by radiations from ytterbium[169], a spectrum of which is shown in Fig. 3, *G*, has been made recently in our laboratory. The related Hurter-Driffield curves are shown in Fig. 3, *H*. The slopes of this curve are similar to those produced when hafnium[175] and cerium-praseodymium[144] are used as the radiation sources. The present status of our experimental work indicates that ytterbium[169] will become useful from a clinical point of view, and for special applications it may become the radiation source of choice.

Since most of the radiographs of the skulls and aluminum step-wedges produced by radiations from the various radioactive isotopes were made on no-screen x-ray film, it seemed desirable to compare these radiographs with roentgenograms produced by radiations from a dental x-ray machine. The Hurter-Driffield curves obtained with 45 kv. and no external filtrations in the beam are shown in Fig. 4, *A*; with 70 kv. and no external filter in Fig. 4, *B*; with 70 kv. and copper and aluminum external filter in Fig. 4, *C*; with 90 kv. and no external filter in Fig. 4, *D*; with 90 kv. and 2 mm. of aluminum external filter in Fig. 4, *E*; and with 90 kv. and copper and aluminum external filter in Fig. 4, *F*. The clinical aspects of these curves are best seen on the density step-wedge curves shown in Fig. 5. The fine dotted line indicates graphically the characteristics of

an ideal roentgenogram. The solid lines and interrupted lines indicate how nearly the radiations produced by various kilovoltage and external filter combinations and by radiations emitted by radioactive isotopes produce a roentgenogram or a radiograph with ideal characteristics. The physical density of the

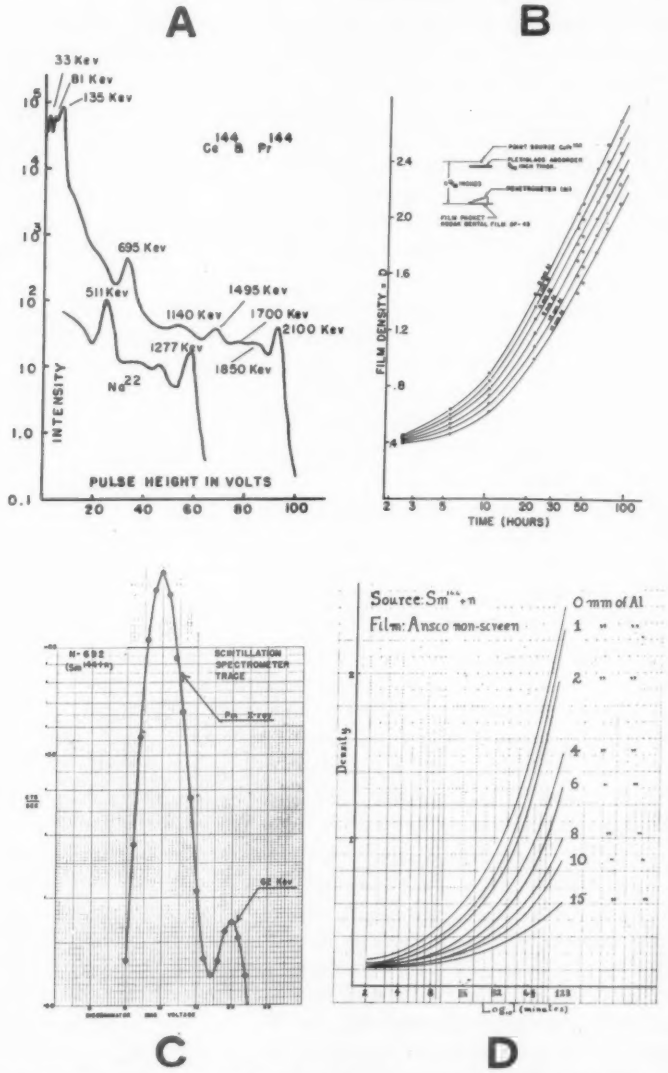



Fig. 3.—*A*, Spectrum of $Ce^{144}$-$Pr^{144}$ as measured by a scintillation spectrometer. *B*, Radiographic densities under various aluminum step-wedge thicknesses, produced by a series of exposure times to radiations from $Ce^{144}$-$Pr^{144}$, plotted as Hurter-Driffield curves. *C*, Spectrum of $Sm^{145}$ as measured by a scintillation spectrometer. *D*, Same as *B*, except that $Sm^{145}$ is substituted for $Ce^{144}$-$Pr^{144}$.

(*Continued on opposite page.*)

1.5 cm. step of the aluminum step-wedge penetrometer is of the same order of magnitude as that of the crown of a molar tooth. The roentgenographic shadow which each produces is therefore equivalent to a reasonable approximation. It is assumed that the crown of a molar with a small carious lesion in it could reasonably have the same physical density as that of 1.0 cm. of aluminum. The density difference on the roentgenogram or radiograph between the 1.0 and 1.5 cm. thicknesses of the aluminum step-wedge penetrometer shadows is represented by the slope of the lines. From a clinical point of view, the steeper the slope, the greater will be the difference in photographic density between a carious

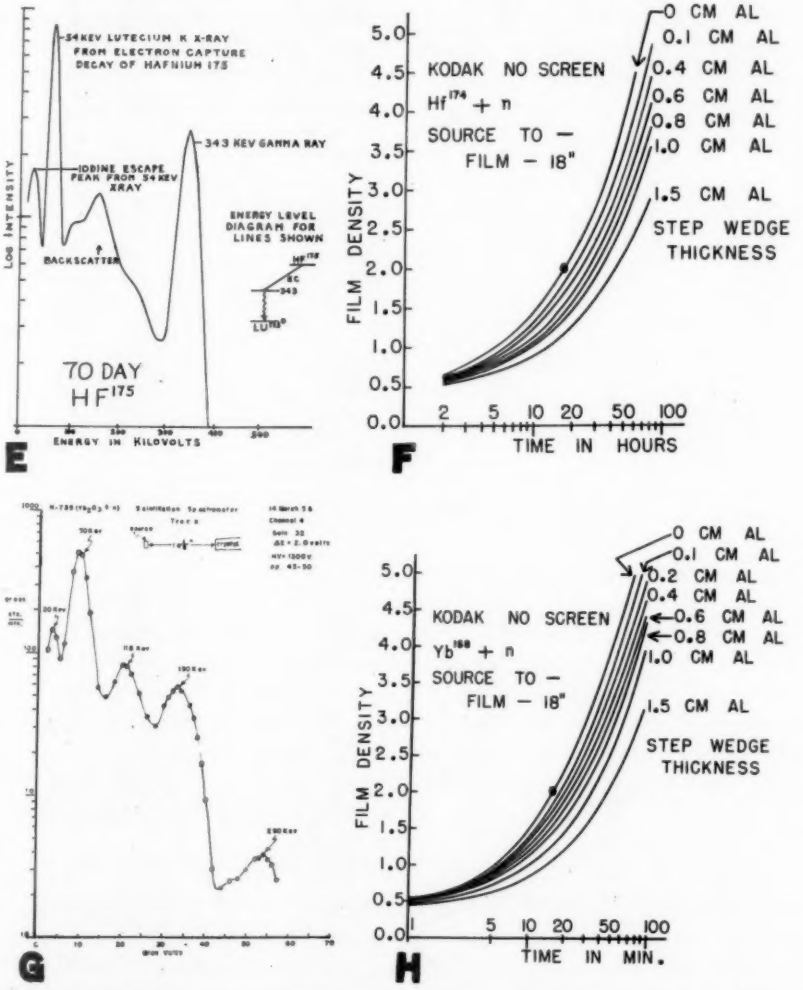



Fig. 3 (Cont'd).—*E*, Spectrum of $Hf^{175}$ as measured by a scintillation spectrometer. *F*, Same as *B* except that $Hf^{175}$ is substituted for $Ce^{144}$-$Pr^{144}$. *G*, Spectrum of $Yb^{169}$ as measured by a scintillation spectrometer. *H*, Same as *B* except that $Yb^{169}$ is substituted for $Ce^{144}$-$Pr^{144}$.

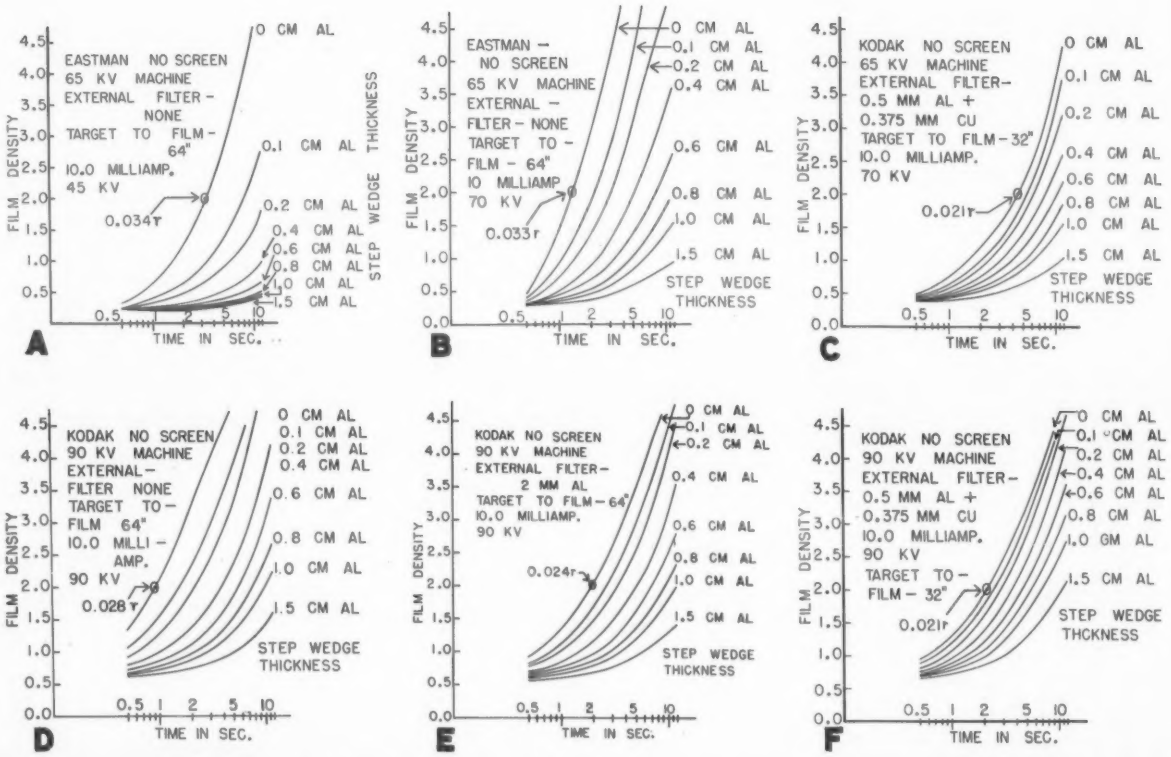



Fig. 4.—*A* to *F*, Roentgenographic densities under various aluminum step-wedge thicknesses, produced by a series of exposure times and plotted as Hurter-Driffield curves when various kilovoltages and external filter configurations are used.

lesion in a tooth and sound tooth structure. If the blackest region of the roentgenogram is restricted to a photographic density of 2, as in this figure, the greatest density difference occurs when radiations from the radioactive isotopes are used. It should be recalled here that their spectral analyses show them to be lacking in the low-energy radiations characteristic of the radiations generated by the x-ray machine. The density difference between 1.0 and 1.5 cm. of aluminum step-wedge penetrometer thickness when radiations from the x-ray machine are used as a source is greatest when the x-ray beam is filtered by external copper and aluminum filters described previously. The least density difference between 1.0 and 1.5 cm. of aluminum step-wedge penetrometer thickness occurs when an unfiltered 45 kv. x-ray beam is used. The density difference in this region is the same, whether a 70 or a 90 kv. unfiltered x-ray beam is used, but it is greater than when a 45 kv. beam is used and less than when copper and aluminum filters are used.

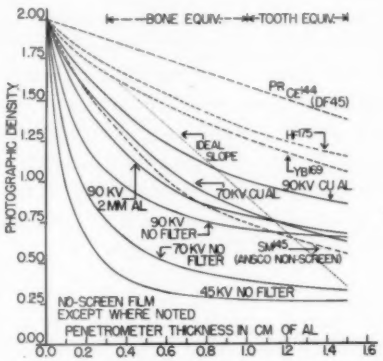



Fig. 5.—Density versus aluminum penetrometer thicknesses for various x-ray and gamma-ray energies.

Roentgenographic shadows produced by aluminum steps between 0.3 and 1.0 cm. in thickness are approximately equivalent to the shadow produced by bone as observed on a clinical roentgenogram. The density difference between the 0.3 and 1.0 cm. steps produced on the roentgenograms is greatest in the case of filtered x-ray beams, whether they be produced by 90 or 70 kv. The least density difference occurs when 45 kv. is used. The density difference between 0.3 and 1.0 cm. aluminum steps when radioactive sources are used is greatest when samarium is the source, followed in descending order by hafnium, ytterbium, and cerium-praseodymium.

## SUMMARY AND CONCLUSIONS

It has been shown that the kilovoltage at which the x-ray machine is operated and the external filtration placed in the x-ray beam affect roentgenographic quality. These investigations indicate that roentgenograms with the best diagnostic characteristics are produced by either a 65 kv. machine operated at 70 kv.

or a 90 kv. machine operated at 90 kv. when the beams are filtered by copper and aluminum. While it is true that such roentgenograms do possess less overall contrast, and therefore may be psychologically less pleasing, a greater amount of information is available in such roentgenograms. Even though the x-ray and gamma-ray radiations emitted by some of the radioactive isotopes discussed in this article are considerably higher in energy than those emitted by either a 65 or a 90 kv. dental x-ray machine, diagnostic radiographs may be produced. The Victoreen "R" Meter indicates that less radiation is required to produce a diagnostic roentgenogram when a filtered beam is used. Of the three filter configurations examined here, 0.375 mm. of copper and 0.5 mm. of aluminum is the best. Spectral analysis with the scintillation spectrometer indicates that the reduction in dosage occurs as a result of the elimination of much of the low-energy part of the white radiations emitted by the dental x-ray machines. If the x-ray beam is unfiltered by added external filtration or is filtered by 0.5 mm. of aluminum added filtration, the radiation dosage required to produce equivalent roentgenographic film densities is less when the radiation from a 90 kv. machine is used in place of the radiation from a 65 kv. machine operated at 70 kv. Under these filter conditions, it would seem that the inclusion of a 90 kv. machine in the diagnostic armamentarium of the general practitioner of dentistry is fully indicated. If the x-ray beam is filtered by 0.375 mm. of copper and 0.5 mm. of aluminum, the radiation dosage required to produce equivalent roentgenographic film densities is the same for both x-ray machines. Under this filter condition, the 65 kv. machine operated at 70 kv. is a reasonable substitute for the 90 kv. machine.

REFERENCES

1. Glasser, Otto, Quimby, E. H., Taylor, L. S., and Weatherwax, J. L.: Physical Foundations of Radiology, ed. 2, New York, 1952, Paul B. Hoeber, Inc.
2. Compton, A. H., and Allison, S. K.: X-rays in Theory and Experiment, New York, 1935, D. Van Nostrand Company, p. 20.
3. Glasser, Otto: Radiation Spectrum. In Glasser, Otto: Medical Physics, Chicago, 1944, The Year Book Publishers, Inc., pp. 1163-1164.
4.(a) Kerst, D. W.: The Betatron, Radiology **40**: 115-119, 1943.
(b) Koch, H. W., Kerst, D. W., and Morrison, P.: Experimental Depth Dose for 5, 10, 15 and 20 Million Volt X-rays, Radiology **40**: 120-127, 1943.
(c) Kerst, D. W.: Betatron. In Glasser, Otto: Medical Physics, Chicago, 1944, The Year Book Publishers, Inc., pp. 27-32.
5.(a) Charlton, E. E., Westendorp, W. F., Dempster, L. E., and Hotaling, George: A New Million-Volt X-ray Outfit, J. Appl. Physics **10**: 375-385, 1939.
(b) Charlton, E. E., Westendorp, W. F., Dempster, L. E., and Hotaling, George: A Million-Volt X-ray Unit, Radiology **35**: 585-597, 1940.
6. Stone, R. S., Livingston, M. S., Sloan, D. H., and Chaffee, M. S.: A Radio Frequency High Voltage Apparatus for X-ray Therapy, Radiology **24**: 153-159, 298-302, 1935.
7. Pool, M. L.: Radioactive X-ray Emitters, Helvet. phys. acta **23**: 178, Supp. 3, 1949.
8. Spangenberg, H. D., Jr.: Production of Roentgenograms by Means of X-ray Radiations From Artificial Radioactive Isotopes: Preliminary Report of an Experimental Study, Engineering Experiment Station News, Ohio State University **20**: 48-50, 1948.
9.(a) Spangenberg, H. D., Jr., and Pool, M. L.: Production of Roentgenograms by X-ray Radiations Obtained From Radioactive X-ray Emitters, J. Am. Dent. A. **47**: 624-630, 1953.
(b) Spangenberg, H. D., Jr., and Pool, M. L.: Production of Clinical Roentgenograms by Means of Compact Radioactive X-ray and Gamma-Ray Sources, J. D. Res. **37**: 920-929, 1958.

10. Trout, E. D., and Kelley, J. B.: Evolution of Equipment for Dental Radiography, J. Am. Acad. Oral Roentgenol., pp. 31-37.
11. Coolidge, W. D.: A Powerful Röntgen Tube With a Pure Electron Discharge, Physiol. Rev. **2**: 409-430, 1913.
12. Ulrey, C. T.: An Experimental Investigation of the Energy in the Continuous X-ray Spectra of Certain Elements, Physiol. Rev. **11**: 401-410, 1918.
13. Ehrlich, Margarete: Scintillation Spectrometry of Low-Energy Bremsstrahlung, J. Res., National Bureau of Standards **54**: 107-118, 1955.
14. Spangenberg, J. D., Jr., Pool, M. L., and Sullivan, R. P.: Scintillation Spectra From Dental X-ray Machines Operated Under Clinical Conditions (Abst.), J. D. Res. **37**: 15-16, 1958.
15. Yale, S. H., and Goodman, L. S.: Reduction of Radiation Output of the Standard Dental X-ray Machine Utilizing Copper for External Filtrations, J. Am. Dent. A. **54**: 354-357, 1957.
16.(a) Mees, O. K. K.: The Theory of the Photographic Process, New York, 1942, The Macmillan Company.
(b) Wilsey, R. B.: Photography: Sensitometry and Densitometry. In Glasser, Otto: Medical Physics, Chicago, 1944, The Year Book Publishers, Inc., pp. 957-963.
17. Wilsey, R. B.: Roentgenography: Films and Papers. In: Glasser, Otto: Medical Physics, Chicago, 1944, The Year Book Publishers, Inc., pp. 1286-1288.
18. Wilsey, R. B., and Pritchard, H. A.: A Comparison of X-ray and White Light Exposure in Photographic Sensitometry, J. Optic. Soc. America **12**: 661-689, 1926.
19. Hodge, Harold, Van Huysen, Grant, Warren, S. L., Bele, W. F., and Wilsey, R. B.: Factors Influencing the Quantitative Measurement of the Roentgen-Ray Absorption of Tooth Slabs. Reprinted as a volume from Am. J. Roentgenol., 1938.

## ROENTGENO-QUESTIONS

*How does one differentiate the incisive fossa (incisive foramen) from a cyst of the incisive canals or from a radicular cyst?*

It is sometimes quite difficult to differentiate these structures roentgenographically. A cyst of one or more of the incisive canals is usually located midway and superior to the roots of the central incisors. Depending on cyst size and ray projection, it may appear to be on either side of the midline and may resemble a radicular cyst. Characteristically, however, a cyst of the incisive canal exhibits an increased area of density in the bone on the lateral aspect but not on the superior and inferior sides of the cyst. Actually, these cysts are within the canal and have expanded it; hence, there is no dense bone above and below the border of the cyst. X-ray studies made from more than one angle are often helpful, as is information gained from vitality tests of the adjacent teeth.

Most cysts associated with the teeth are rather round in appearance, and there is an even, definite outline around the entire circumference of the cyst. In addition, the periodontal membrane space of the associated root will be lacking at the site of the cyst. Cysts of the incisive canal are not actually associated with the teeth but arise from epithelial rests within the canal. The periodontal membrane spaces of the associated teeth should be observable unless burned out by overexposure. An additional film taken at a reduced exposure time is often helpful in revealing the intact space. Differentiation of an incisive canal cyst from a normal large incisive canal is often difficult. Subjective symptoms of discomfort, swelling, and perhaps a "salty taste" are helpful. Aspiration of fluid from the questionable area is indicative of a cyst. If neither objective nor subjective symptoms were present, the area could be observed periodically for roentgenographic or clinical changes.

---

The American Academy of Oral Roentgenology solicits from the readers of ORAL SURGERY, ORAL MEDICINE AND ORAL PATHOLOGY any questions which deal with technical or interpretive aspects of oral roentgenology. These questions should be sent directly to the editor of this section, Dr. Arthur H. Wuehrmann, School of Dentistry, University of Alabama Medical Center, Birmingham, Alabama; the editor will distribute them for reply to a suitable group within the Academy. Questions, with the answers, will be published at as early a date as possible in "Roentgeno-Questions." Questions, especially those of an interpretive nature, should ordinarily be accompanied by good-quality roentgenograms and a pertinent history. The names of the questioner and the respondent will not be published.

## ROENTGENO-ODDITIES

### Film Reticulation

THE three films shown here demonstrate varying degrees of reticulation. This is perhaps best described as a weblike formation or appearance or as a kind of network or cracked appearance in the emulsion. Such reticulation is caused by placing films that have been processed in a moderately warm solution into a second solution which has a considerably lower temperature. The result of this action is a sudden solidifying of an almost liquid emulsion with a tendency to congeal into multiple centers and thus pull away from the areas

Each month this section will bring to the readers of ORAL SURGERY, ORAL MEDICINE AND ORAL PATHOLOGY one or more roentgenograms which demonstrate unusual, unexpected, rare, or bizarre roentgenographic changes. These roentgenograms will be accompanied by an explanation or by words of inquiry regarding the particular change. All films used in this section will be accepted with the understanding that 2 by 2 or 3¼ by 4 inch slides or glossy photographs of the films will be made available to interested readers through the editor of the American Academy of Oral Roentgenology at the individual's expense. The cost will involve only the photographer's charges. Each slide or print will give credit to the donor. Interesting roentgenograms are solicited from all sources. Please be certain to identify your films properly so that they can be returned. All material for publication should be submitted to Dr. Arthur H. Wuehrmann, University of Alabama School of Dentistry, Medical Center, Birmingham, Alabama.

peripheral to these centers. The degree of reticulation shown in the upper right-hand and lower films was produced deliberately for purposes of demonstration and emphasis. The amount of reticulation found in the upper left-hand film is quite common.

*Arthur H. Wuehrmann*
*University of Alabama*

# ORAL PATHOLOGY

. . . . . .

## PRENATAL FACTORS IN ORAL PATHOLOGIC CONDITIONS*

*Seymour J. Kreshover, D.D.S., M.D., Ph.D.,** Bethesda, Md.*

THE category of disabilities recognized as congenital defects needs no introduction to this audience. Nevertheless, while accepting the marvelous perfection of the newborn baby as a matter of routine, we have all at one time or another pondered over the many things that could have gone wrong in the development of this complex organism. The true magnitude of the problem of congenital malformations can best be shown by surveys of incidence. In 1950, the Office of Vital Statistics reported that for the first three months of that year the neonatal mortality rate from malformations alone among infants weighing 2,500 grams or less at birth was about one and one-half times the rate for all causes of death in this group.[1] Even this, however, probably represents a low figure of incidence, since it was based on death certificate information which would not have included many congenital anomalies that are quite compatible with life and which would have included many babies who had not been examined at autopsy for internally occurring defects. In addition, many defects might have been complicated or camouflaged by superimposed disease conditions and thus overlooked in clinical diagnosis. A later survey of incidence (at the Sloane Hospital for Women in New York City), based on almost 6,000 deliveries in which the fetuses weighed over 500 grams, showed 7.5 per cent with malformations.[2] It is particularly significant that of the abnormalities found among liveborn infants, less than one-half were suspected or noted at time of birth.

Our very limited knowledge of congenital abnormalities is well illustrated by the frequent inability of obstetricians and pediatricians to provide satisfactory answers for parents of abnormal children when they seek counsel on such questions as: "Is it safe for us to have another child?" or "What caused our baby to be abnormal?" This difficulty in providing answers may actually be indicative of some progress, however, since it was not too many years ago that all congenital defects were simply dismissed as hereditary accidents. Although advances based on studies of man will probably continue to be slow in coming

*Seventh Herman L. Reiss Memorial Lecture of the New York Institute of Clinical Oral Pathology, Inc., presented at the New York Academy of Medicine, Oct. 27, 1958.

**Associate Director, National Institute of Dental Research, National Institutes of Health, Public Health Service, United States Department of Health, Education, and Welfare.

due to the difficulty of obtaining complete medical and family histories for analysis, the current emphasis on laboratory experimentation is contributing significant information with respect to congenital anomalies.

In attempting to understand the many and complex mechanisms that underlie developmental abnormalities, it is necessary to look at the very beginning of embryonic life. Initiated by fertilization of the ovum, a process of organogenesis and development begins which is immediately subject to two avenues of influence—that mediated through the nuclear substance of the fertilized egg (the hereditary factor) and that operating via the environment (the nongenetic factor).

In considering hereditary transmission of developmental defects, it should be recalled that the nuclear material of the fertilized ovum contains the chromosomes which, in turn, carry the genes. In man, each gamete contributes twenty-four chromosomes to the total of forty-eight which characterizes the zygote. Since each set of chromosomes—that contributed by the male and that contributed by the female—contains a full assortment of genes, there is provided a potential for complete development. Although it may be said that each member of a pair of genes has a similar principal function as related to some trait, characteristic, or phase of organ system development, the two genes may on occasion differ in their ability to produce identical results. Whereas a person carrying a pair of genes that tends to produce identical results is homozygous with respect to the particular trait, structure, or function that these genes determine, a person who carries a pair of genes that may produce different results is heterozygous, and the complementing genes will be respectively dominant and recessive in action. In the event of a pathologic trait being recessive, any mating with a person possessing a normal, dominant gene for that same characteristic will result in offspring, 50 per cent of whom are heterozygous carriers of the recessive pathologic trait (with an outwardly normal appearance) and 50 per cent of whom are homozygous normal persons with no hidden pathologic trait. It should be emphasized that in an average population group, this is the mating most likely to occur, and that marriage to another heterozygous person carrying the same recessive pathologic trait would be most unlikely on the basis of pure chance alone.

Not only can hereditary effects be modified by, for example, a skip in the transfer of an abnormal trait past one generation due to a reduced ability of the defective gene to express itself but a defect may be transmitted as a simple predisposition or tendency to a disease, in which case no abnormality would be expressed unless activated by an environmental factor (as, for example, a predisposition to allergy being manifested only after exposure or sensitization to an allergen). Another important modification of genetic transference is that related to sex-linkage. Of the forty-eight chromosomes comprising the fertilized human ovum, only forty-six can be arranged in twenty-three homologous pairs, the remaining pair being the sex chromosomes. In the female, both of these so-called X chromosomes are large, of equal size, and carry many genes, whereas in the male the two chromosomes are of unequal size, one being a large X chromosome similar to the female chromosomes and the other a smaller, so-called Y

chromosome which carries fewer genes. Such a dissimilarity of paired chromosomes becomes extremely important in the case of a pathologic gene located in the X chromosome of the male, since the nonhomologous paired gene in the Y chromosome would be incapable of suppressing the abnormal gene. On the other hand, in the homologous X chromosomes of the female, a recessive, abnormal gene in one of the sex chromosomes can be checked if its paired gene is a dominant, normal one. In such an instance, the hereditary pathologic trait, although transmitted through the female, would appear only in the male members of a family. It is well to be reminded at this point that hereditary characters may also be dependent upon the combined action of several genes. For example, if abnormal genes are present in a number of chromosomes, they will associate and dissociate in different matings according to the laws of chance and thereby lessen the prospect of the pathologic trait becoming manifest.

Perhaps located somewhere in the unexplored region between pure hereditary and pure environmental influences are such factors as may be responsible for (1) the increased incidence of malformed offspring in multiple births, (2) the relative frequency of malformations in offspring conceived in the earliest and latest years of a mother's reproductive life, and (3) the greater percentage of developmental anomalies in the white race as compared with nonwhite races. Such observations as these, coupled with the fact that many types of environmental agents can be shown experimentally to produce malformations identical with those produced by defective genes, add to the difficulty of determining the specific role played by heredity. Nevertheless, recent years have witnessed a growing realization that many, and perhaps most, congenital deformities are due to environmental factors and can no longer be dismissed arbitrarily as genetic accidents. Seemingly, a vast new field of pathology is being opened for which methods of medical and dental control must be sought.

To begin to understand the important influence of environment on intrauterine development, it is necessary to recognize that nongenetic factors can operate at any period between the times of conception and birth. It should be emphasized, however, that although a vast array of mechanical, chemical, nutritional, infectious, and metabolic factors can effect a change in an organism of normal genetic make-up, there is probably a continual interplay with heredity as it exerts a modifying influence on host susceptibility. It should further be recognized that not only may a single type of injurious agent cause different types of developmental arrest or abnormality but that a specific type of malformation may be caused by a wide variety of environmental factors. In the case of so-called time-specificity of action, there exists ample evidence that the period of gestation during which a noxious agent is applied or becomes active may well determine the nature of the embryonal reaction. Thus, in roentgen-ray irradiation, different types of deformity can be induced, depending upon which organ systems or tissues are undergoing development at the time of exposure.[3] It must be emphasized, however, that such specificity of reaction is reproducible only if the dosage of the injurious agent is controlled, for although an organ or tissue may be most sensitive during a limited period of its development its response is not necessarily limited to this period. The relationship of host to

environment is further complicated by the fact that certain agents are capable of eliciting characteristic responses. Thus, by exerting their effect on different processes or phases of embryonic development, one injurious mechanism, such as riboflavin deficiency operating at a specific time of pregnancy, can cause a typical and reproducible syndrome of developmental abnormalities characterized by deformed long bones, syndactylia, brachydactylia, shortened mandible, and cleft palate,[4, 5] whereas another agent, such as trypan blue administered during the same stage of pregnancy, will cause a different but characteristic picture of hydrocephalus, exencephalia, spina bifida, and eye defects.[6] While recognizing this phenomenon of agent specificity, it should be clearly understood that different types of noxious agents can also cause identical defects even though applied at the same stage of organogenesis. An example of such nonspecificity, wherein a variety of mechanisms or injurious agents can be related to a particular deformity, is cleft palate produced in rats and mice by anoxia,[7] nutritional deficiency,[8] endocrine change,[9] and nitrogen mustard administration.[10] In general, however, it may be said that the incidence and type of defect, both oral and extraoral, will vary with the agent used, its dosage, the stage of gestation when it is applied, and the genetic constitution of the host animal.

It is only within recent years that any appreciable attention has been directed to in utero effects on mouth and tooth development. As previously suggested, the common deformities of harelip and cleft palate have presented a confusing history with respect to their etiology. Although, in some instances, these deformities are unmistakably related to defective genetic composition, a considerable proportion are undoubtedly due to environmental change. Only recently, however, has such a varied causal relationship been recognized. All too frequently, the pendulum of scientific opinion has swung to extremes, and where theories of heredity prevailed there has reigned confusion regarding its mode of transmission. As an example, one investigator, after compiling and evaluating data from three previously published surveys by independent authors, concluded that harelip and cleft palate are inherited in man as a double-recessive trait, one gene lying in the sex chromosome and the other being autosomal.[11] In contrast, another report, based on a series of 625 propositi, suggested that harelip, as well as the combined deformity of harelip and cleft palate, is always genetically determined by a conditioned dominance with sex limitation to males.[12] Interestingly enough, this same study concluded that when it occurs alone cleft palate is usually nonhereditary in origin, but when it is transmitted by defective genes it is mediated by a simple dominance with sex limitation to females.

Paralleling the dogmatic views expressed by many proponents of the hereditary theory of harelip and cleft palate etiology have been the equally opinionated views of so-called environmental theorists.[12] Thus, emotional disturbances related to factors of mental stress and so-called "shock" during pregnancy were long considered a primary cause of cleft palate. Another popular theory of etiology was physical interference with palatal closure caused by a fetal finger

being in a mouth-sucking position. Other dogmatically expressed theories have implicated an inadequate vascular supply to the palatal region and amniotic bands caught in the lines of embryonic closure.

Although clinical studies are most essential to elucidate the origin of harelip, cleft palate, and other defects of oral development, some of the more significant advances in knowledge have been gained by the experimental method. One such study, which has contributed important information on the interrelated roles of heredity and environment, is that of Walker and Fraser.[13] Studying the relationship of cortisone to cleft palate deformities, these investigators demonstrated a 100 per cent incidence of clefts in one strain of mice following daily intramuscular injections of cortisone acetate between the eleventh and fourteenth days of gestation, whereas another strain of the same animal species showed a markedly lower (1:5) incidence. Although this investigation clearly demonstrates both genetic and environmental influences, it also serves to emphasize that cleft palate deformities may be anatomically identical, regardless of etiology (that is, an exact resemblance existing between deformities caused by defective genetic composition and those caused by an environmental modification). Reference has already been made to a variety of other experimental methods by which cleft palate can be produced. In all such experimental studies, it is important to understand the time sequence of palate development. As shown by Walker and Fraser, the palatine shelves of mice, which initially lie in a vertical plane on either side of the tongue, normally move into a horizontal plane so as to extend across the dorsum of the tongue and fuse in the midline on, or shortly after, the fifteenth gestational day.[14]

In an effort to contribute further to our understanding of cleft palate etiology, a study was recently initiated to evaluate more thoroughly the factors of amniotic sac compression and maternal-fetal vascular supply. Although previous studies have suggested that amniotic fluid loss can cause palatal clefts by reason of pressure on the fetus with consequent bulging of the tongue into the undeveloped palate,[15] this concept of pathogenesis warrants further clarification. By means of a midline abdominal incision, the uteri of a number of rats, 14 to 15 days in gestation, were exposed and a needle puncture wound was made through the amniotic sac of selected embryos. Other fetuses in each operated animal served as controls. Limited observations to date have confirmed the reports that a significant relationship exists between amniotic sac puncture and cleft palate. Presumably, a loss of amniotic fluid can cause compression of the fetal head against the thorax, with consequent bulging of the tongue into the roof of the mouth. Such a concept of pathogenesis is conjectural, however, until more is known about the degree of fluid loss. Exploring this question, quantitative measurements were made of amniotic fluid taken from control and experimental fetuses. Although based on a limited number of observations, there is good evidence that the loss of fluid through punctured amnions is substantial and thus capable of causing amniotic sac pressure directly upon the fetus. Another interesting finding, not previously reported, is the high incidence of limb deformities in experimental fetuses. Whether this constitutes sufficient supporting evidence for the "pressure" theory is a moot question.

With reference to adequacy of fetal blood supply as an etiological factor in congenital abnormalities, preliminary observations in rats have shown a high incidence of resorption subsequent to temporary occlusion of the uterine and uteric arteries. Since fetal resorption was the predominant change, even under varied conditions of duration of circulatory arrest (fifteen minutes to four hours) and stage of gestation (seven to fifteen days), it would seem that this method of inducing an anoxic condition is not contributory to anomalous development. Presumably, a significant difference in the degree of anoxia, as well as the animal species studied, accounts for the high incidence of cleft palate deformities in mice reported by Ingalls, Curley, and Prindle.[7]

Although harelip and cleft palate represent the more serious types of abnormalities affecting oral tissues, developmental defects involving the teeth per se are of importance not only in terms of esthetics but also as a means for gaining more information on congenital defects in general. Many reports are to be found in the literature relating a wide variety of metabolic and other disturbances to tooth abnormalities. However, the vast majority of these studies, such as those dealing with fluoride toxicity,[16] endocrine imbalance,[17] and vitamin deficiencies,[18, 19] are concerned with the postnatal period of dental development. It is, therefore, not clearly established whether such disturbances to the mother during pregnancy can have similar effects on the developing dental tissues of the fetus in utero. Among the few earlier investigations of this question are those of Mellanby,[20] who observed abnormal dental development in the offspring of rats that were rendered deficient in vitamin A, and Diamond and Weinmann,[21] who called attention to maternal syphilis as an etiological factor in abnormal amelogenesis. In other studies, Sheldon, Bibby, and Bales[22] noted prenatally occurring defects in five of thirty-four individuals studied, and Stein[23] reported eight cases of enamel hypoplasia in deciduous teeth of children. More recently, the studies of Warkany[5, 24] have excited a renewed and even greater interest in the subject of congenital abnormalities. From such reports as these, it seems quite reasonable to expect that any disturbance in the highly specialized function of amelogenesis and dentinogenesis occurring during the prenatal period might be indicative of a more widespread fetal response to the particular injurious agent operating at the time. By the same token, the teeth might also contribute much-needed information on the subject of the placenta as a barrier to or pathway for transfer of various injurious agents from mother to fetus. In order to pursue these several questions, a series of studies utilizing both human and experimental animal material was carried out during the past few years.[25, 30-32]

In a study of thirty-five infants, ranging from premature stillborns to 2½-month-old babies, twenty-seven (77 per cent) showed abnormalities of tooth formation and eight (23 per cent) were negative.[25] Changes varied from early cystic degeneration of ameloblasts and odontoblasts, with temporary arrest of odontogenesis and formation of hyperplastic masses of organic enamel matrix, to complete cessation of enamel formation. On the basis of evidence provided by length of gestation, duration of life, patterns of enamel and dentine apposition, and micrometer measurements, it was possible to categorize the cases into

seven (26 per cent) of prenatal onset, fifteen (55 per cent) that occurred during the neonatal period, four (15 per cent) that were of postnatal occurrence, and one (4 per cent) that was related to both the prenatal and the postnatal periods. Of additional significance was the fact that maternal, obstetrical, pediatric, and necropsy histories and examinations made it possible in many instances to correlate the factor or factors responsible for the dental abnormality. The frequent occurrence of abnormal tooth development not only in the offspring of mothers with abnormal pregnancies but also in the children of mothers with seemingly normal pregnancies as well as the reverse situation of normal tooth formation in cases of complicated pregnancy, attests to the nonspecific nature of congenital dental defects and the difficulty of establishing cause-effect relationships in man. Nevertheless, it is significant to note that the incidence of congenital dental defects is probably greater than heretofore suspected.

With specific reference to dental defects of hereditary origin, rather common anomalies are related to the number as well as to the form of teeth, perhaps most frequent in occurrence being congenital absence of the maxillary second incisors. Another genetically determined abnormality, presumably transmitted as an autosomal dominant trait, is dentinogenesis imperfecta.[26] This disease is frequently associated with osteogenesis imperfecta, and its characteristic tooth changes reflect a general pattern of mesenchymal disturbance. Amelogenesis imperfecta is still another hereditary condition which is transmitted as a dominant Mendelian characteristic.[27] Often confused in terminology, this defect has been variously described in the literature under such terms as "hereditary brown opalescent teeth" and "hereditary enamel hypoplasia."

An example of sex-linked inheritance is ectodermal dysplasia, which is frequently characterized by partial or complete anodontia and defective development of such ectodermal structures as the sweat glands and hair follicles.[28] Gargoylism is another example of a genetically determined disorder which is transmitted by a single recessive gene, is sometimes sex-linked,[29] and may show neonatally developed abnormalities of enamel formation.[25] The basic metabolic disturbance in this disease results in the accumulation of a lipoidlike material in cells and organs and a characteristic syndrome of abnormalities which include mental deficiency, malformed skull, prominent supraorbital ridges, depressed bridge of nose, enlarged tongue, short neck, corneal opacity, and kyphosis.

In order more adequately to evaluate the subject of environmental maternal influences on fetal dental development, several prenatally occurring disturbances, such as pyrexia, hyperglycemia, and viral infections, were studied in experimental animals.[30-32] In the case of fever, which is a common accompaniment of many disease states and thus is implicated as a possible postnatal cause of enamel hypoplasia, a definite prenatal cause-and-effect relationship was found in rats.[30] Alloxan-induced diabetes resulted in a similar picture of abnormal odontogenesis.[31] In contrast to these fetal changes, the establishment of a vaccinia virus infection in pregnant rabbits failed to produce any dental disturbances in the young, although the maternal animals developed severe oral lesions.[32] It is perhaps significant that in the latter study no evidence could be found of transplacental infection.

Although considerably more study than has been reported here is required to elucidate the obviously complex mechanisms involved in congenital oral pathologic conditions, ample evidence is now available to demonstrate that this category of developmental disturbances is not simply a matter of chance hereditary occurrence. Rather, an important and clear-cut relationship to environmental factors is now seen to exist. The consequent implications in terms of professional responsibility to explore to the fullest any and all means for prevention of congenital malformations are unmistakable. To approach this goal, one must continue to give major attention not only to experimental studies but also to the analysis of records assembled through carefully obtained clinical histories and examinations.

REFERENCES

1. Relation of Weight at Birth to Cause of Death and Age at Death in Neonatal Period: United States Early 1950, National Office of Vital Statistics, vol. 39, 1956.
2. McIntosh, R., Merritt, K. K., Richards, M. R., Samuels, M. H., and Bellows, M. T.: The Incidence of Congenital Malformations: A Study of 5,964 Pregnancies, Pediatrics 14: 505, 1954.
3. Wilson, J. G.: Differentiation and the Reaction of Rat Embryos to Radiation, J. Cell. & Comp. Physiol. 43: 11, 1954.
4. Warkany, J.: Manifestations of Prenatal Nutritional Deficiency, Vitamins & Hormones 3: 73, 1945.
5. Warkany, J., and Deuschle, F. M.: Congenital Malformations Induced in Rats by Maternal Riboflavin Deficiency, J. Am. Dent. A. 51: 139, 1955.
6. Gillman, J., Gilbert, G., and Gillman, T.: Preliminary Report on Hydrocephalus, Spina Bifida and Other Congenital Anomalies in the Rat Produced by Trypan Blue; the Significance of These Results in Interpretation of Congenital Malformations Following Maternal Rubella, South African J. M. Sc. 13: 47, 1948.
7. Ingalls, T. H., Curley, F. J., and Prindle, R. A.: Anoxia as a Cause of Fetal Death and Congenital Defect in the Mouse, Am. J. Dis. Child. 80: 34, 1950.
8. Nelson, M. M.: Production of Congenital Anomalies in Mammals by Maternal Dietary Deficiencies, Pediatrics 19: 764, 1957.
9. Fraser, F. C., Kalter, H., Walker, B. E., and Fainstat, T. D.: The Experimental Production of Cleft Palate With Cortisone and Other Hormones, J. Cell. & Comp. Physiol. 43 (Supp. 1): 237, 1954.
10. Haskin, D.: Some Effects of Nitrogen Mustard on the Development of External Body Form in the Fetal Rat, Anat. Rec. 102: 493, 1948.
11. Fortuyn, A. B. D.: Inheritance of Harelip and Cleft Palate in Man, Genetica 17: 349, 1935.
12. Fogh-Andersen, P.: Inheritance of Harelip and Cleft Palate, Nyt Nordisk Forlag, Copenhagen, 1942, Arnold Busch.
13. Walker, B. E., and Fraser, F. C.: The Embryology of Cortisone-Induced Cleft Palate, J. Embryol. & Exper. Morphol. 5: 201, 1957.
14. Walker, B. E., and Fraser, F. C.: Closure of the Secondary Palate in Three Strains of Mice, J. Embryol. & Exper. Morphol. 4: 176, 1956.
15. Trasler, D. G., Walker, B. E., and Fraser, F. C.: Congenital Malformations Produced by Amniotic-Sac Puncture, Science 124: 439, 1956.
16. Smith, M. C., and Lantz, E. M.: Experimental Production of Mottled Enamel, University of Arizona Tech. Bull. No. 45, p. 327, 1933.
17. Thoma, K. H.: Oral Pathology, ed. 3, St. Louis, 1950, The C. V. Mosby Company, p. 21.
18. Wolbach, S. B., and Howe, P. R.: The Incisor Teeth of Albino Rats and Guinea Pigs in Vitamin A Deficiency and Repair, Am. J. Path. 9: 275, 1933.
19. Klein, H.: Etiology of Enamel Hypoplasia in Rickets as Determined by Studies on Rats and Swine, J. Am. Dent. A. 18: 866, 1931.
20. Mellanby, H.: The Effect of Maternal Dietary Deficiency of Vitamin A on Dental Tissues in Rats, J. D. Res. 20: 489, 1941.
21. Diamond, M., and Weinmann, J. P.: The Enamel of the Human Teeth, New York, 1940, Columbia University Press.
22. Sheldon, M., Bibby, B. G., and Bales, M. S.: Relationship Between Microscopic Enamel Defects and Infantile Debilities, J. D. Res. 24: 109, 1945.

3. Stein, G.: Enamel Damage of Systemic Origin in Premature Birth and Diseases of Early Infancy, Am. J. Orthodontics & Oral Surg. **33**: 831, 1947.
4. Warkany, J.: Congenital Malformations and Pediatrics, Pediatrics **19**: 725, 1957.
5. Kreshover, S. J., Clough, O. W., and Bear, D. M.: A Study of Prenatal Influences on Tooth Development in Humans, J. Am. Dent. A. **56**: 230, 1958.
26. Hursey, R. J., Witkop, C. J., Miklashek, D., and Sackett, L. M.: Dentinogenesis Imperfecta in a Racial Isolate With Multiple Hereditary Defects, ORAL SURG., ORAL MED. & ORAL PATH. **9**: 641, 1956.
27. Thoma, K. H.: Oral Pathology, ed. 3, St. Louis, 1950, The C. V. Mosby Company, p. 16.
28. Thadani, K. I.: A Toothless Type of Man, J. Hered. **12**: 87, 1921.
29. Ellis, R. W., Sheldon, W., and Capon, N.: Gargoylism (Chondro-osteodystrophy; Corneal Opacities; Hepato-splenomegaly and Mental Deficiency), Quart. J. Med. **29**: 119, 1936.
30. Kreshover, S. J., and Clough, O. W.: Prenatal Influences on Tooth Development. II. Artificially Induced Fever in Rats, J. D. Res. **32**: 565, 1953.
31. Kreshover, S. J., Clough, O. W., and Bear, D. M.: Prenatal Influences on Tooth Development. I. Alloxan Diabetes in Rats, J. D. Res. **32**: 246, 1953.
32. Kreshover, S. J., Clough, O. W., and Hancock, J. A.: Vaccinia Infection in Pregnant Rabbits and Its Effect on Maternal and Fetal Dental Tissues, J. Am. Dent. A. **49**: 549, 1954.

## SIALOLITHIASIS OF A MINOR SALIVARY GLAND

*A. P. Chaudhry, B.D.S., M.S., Ph.D., R. J. Gorlin, D.D.S., M.S., and D. H. Reynolds, B.S., Minneapolis, Minn.*

SIALOLITHIASIS of the major salivary glands is not an uncommon condition. It is most frequently encountered in the submaxillary duct and gland and, next in order of frequency, in the parotid and sublingual glands. Rarely, stones are found in the minor salivary glands. A single case was reported in 1955 by Lighterman.[1] This occurred in the mucosa of the cheek in close proximity to the mucobuccal fold opposite the lower right first premolar. We saw an almost identical case and, because of its rarity, we considered it worth reporting.

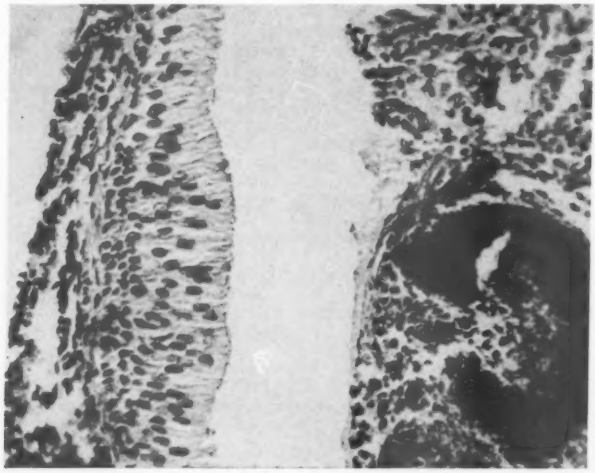


Fig. 1.—Photomicrograph showing hyperplastic pseudostratified columnar epithelium lining the dilated duct filled with concretions.

A biopsy specimen, 0.5 cm. in diameter, was received by the Pathology Laboratory of the University of Minnesota School of Dentistry for microscopic diagnosis. This specimen had been removed from the oral mucosa of a 70-year-

From the Division of Oral Pathology, School of Dentistry, University of Minnesota.

old white woman. The lesion was located midway between the gingival margin and the mucobuccal fold opposite the root of the lower right first premolar. It was described as being a firm, sessile nodule which was nonadherent to the underlying periosteum. It had caused the patient no trouble and was covered with normal intact mucosa. Roentgenographic examination showed no apparent pathologic condition of the teeth and bone in this area. A systemic review of the patient's medical history was noncontributory. The lesion was excised under local anesthesia and was fixed in 10 per cent formalin.

Grossly, when the specimen was cut, concretions were apparent. Microscopically, the tissue was composed chiefly of mucous glands with dilated ducts. One of the extremely dilated ducts was lined with pseudostratified columnar epithelium with varying degress of hyperplasia (Fig. 1). The lumen was filled with cellular debris composed of desquamated epithelial cells and inflammatory cells of the polymorphonuclear leukocyte type. Furthermore, several concretions were also present in the lumen (Fig. 2). It appeared from the microscopic examination that cellular degeneration had resulted in the formation of organic matrix in which calcium salts were being deposited. The calcified part of the concretions stained blue, in contrast to the eosinophilic organic portion.

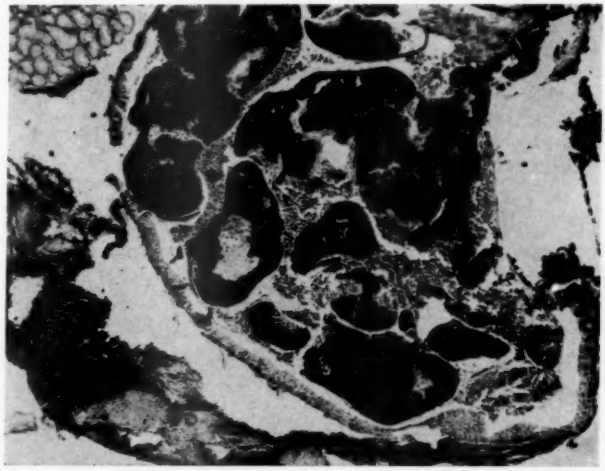


Fig. 2.—Photomicrograph showing the lumen of the duct filled with small calcified masses and cellular debris. Note close proximity of the mucous gland to the duct.

## DISCUSSION

The case just described impressed us for two reasons. First, this is the second case of sialolithiasis of the minor salivary gland published in the literature. Strangely enough, each case occurred in the region of the lower right first premolar in a woman past middle age. This could be coincidental, or it may prove to have some significance when more cases are available for study.

Second, it is not surprising to observe metaplasia of a glandular type of epitheli um into a squamous variety under conditions of vitamin A deficiency or chroni inflammation due to partial obstruction, but the transformation into pseudo stratified columnar epithelium seen in this case is most unusual.

REFERENCE

1. Lighterman, I.: Sialolithiasis of a Minor Salivary Gland, ORAL SURG., ORAL MED. & ORAL PATH. 8: 143-145, 1955.

# ANAPLASIA

## Report of a Case

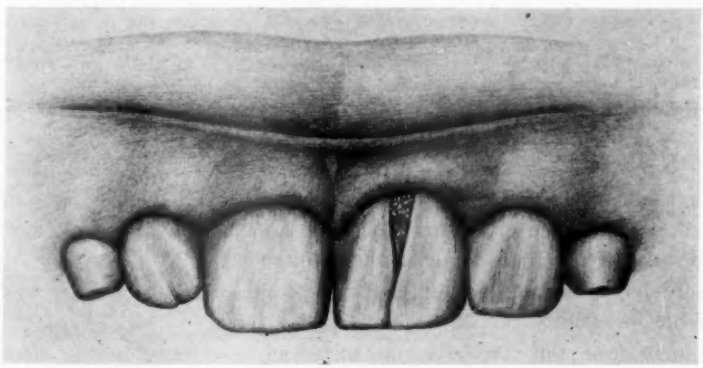
*Woodrow S. Monica, D.M.D., Orange, N. J.*

ANAPLASIA is the continuous, defective development of enamel from the incisal edge or cuspal tip to the cementoenamel junction. It may be complete, in which case the entire crown is devoid of enamel,[1] or it may be partial if only a segment of ameloblasts is affected.

The following case illustrates a continuous defective development of a segment of ameloblasts.

### CASE REPORT

A hypoplastic permanent incisor of a 10-year-old boy is shown in Figs. 1 and 2. The defect starts at the incisal edge as a narrow, linear depression and widens to about 2 mm. at the cementoenamel junction. It is 10 mm. long, and the cervical half contains decayed material that is almost flush with the labial surface. Although the tooth is vital, it has never caused pain. The remaining permanent incisors are well formed, white, and sound. An enamel pearl has been deposited at the cervical part of the tooth (Fig. 2).



*(Drawing by M. Barr.)*

Fig. 1.

The patient is well developed, healthy, and bright. His mother had a normal pregnancy and delivery. The patient was breast- and bottle-fed. Both the patient and his mother have always lived in a low-fluoride area (less than one part of fluorides per 1,000,000

parts of water). The boy has never had convulsions, severe vomiting, diarrhea, whooping cough, diphtheria, smallpox, scarlet fever, or mumps. He does not have a history of hypothyroidism, hypoparathyroidism, fluorosis, rickets, or congenital syphilis. He had measles when he was 4 years old.

The patient's brothers, parents, grandparents, uncles, and aunts do not have teeth with hypoplastic enamel.

The superior primary central incisors erupted at 7 months; they were well formed and white. The superior permanent central incisors erupted at 7 years of age.

Fig. 2.

When he was 1 year old, the patient fell down a flight of stairs. At 1½ years of age, he tumbled off a low porch. His deciduous teeth were not loosened in the fall; they never discolored or caused fistulas.

COMMENT

The enamel defect in the case just described extended the entire length of the crown to the depth of the dentine. The organic material in the defect resembled decayed dentine. It did not look like bone.

The defect was not inherited, and it was not caused by disease, endocrine dysfunction, or fluorosis.

Trauma from the two falls may have caused stresses in the ameloblasts during matrix formation.[2] If this were the case, the ameloblasts may have deposited a hyaline-like material.[3] On the other hand, connective tissue may have invaded the defect and deposited cementum.

The root develops after the enamel and dentine reach the future cemento-enamel junction. The outer and inner epithelial layers of the enamel organ

form Hertwig's sheath. This sheath molds the root-forming odontoblasts. After the first layer of root dentine is formed, the pulpal connective tissue proliferates and separates the epithelial root sheath into strands of cells. When this happens, the epithelium is also pushed from the newly formed dentine so that only connective tissue borders the dentine. These connective tissue cells, in turn, differentiate into cementoblasts.

If aberrant epithelial cells remain in contact with the newly formed root dentine, they may revert to their ameloblastic activity and deposit enamel "droplets" or "pearls."[4]

REFERENCES

1. Colby, R. A.: Color Atlas of Oral Pathology, Philadelphia, 1956, J. B. Lippincott Company, p. 43.
2. Hodson, J. J.: An Investigation Into the Microscopic Structure of the Common Forms of Enamel Lamellae, ORAL SURG., ORAL MED. & ORAL PATH. 6: 305-317, 1953.
3. Kerr, D. A.: Histological Changes in the Enamel Organ Responsible for Enamel Hypoplasia, Am. J. Orthodontics & Oral Surg. 30: 673-679, 1944.
4. Orban, B.: Oral Histology and Embryology, ed. 3, St. Louis, 1953, The C. V. Mosby Company.

310 MAIN ST.

# MALIGNANT MELANOMA OF THE ORAL CAVITY

## Report of a Case

*A. P. Chaudhry, B.D.S., M.S., Ph.D., Roger J. Burke, D.D.S., M.S.D., and R. J. Gorlin, D.D.S., M.S., Minneapolis, Minn.*

### INTRODUCTION

ONLY 105 cases of primary malignant melanoma of the oral cavity were reported in the literature from 1857 to 1957.[1] The present case was included in that number. Since this patient had been followed at the School of Dentistry of the University of Minnesota from the time the disease was diagnosed until her death, it was considered desirable that the case be published.

### CASE REPORT

The patient, a 64-year-old white woman, could not recall the exact duration of pigmentation of her upper alveolar mucosa. However, she became aware of it three years prior to biopsy. The pigmentation was insidious in onset but gradually increased in size. The patient had brought it to the attention of her dentist two years previously. In December, 1956, she noticed a tumor mass at the site of pigmentation. The mass was dark blue in color, very soft in consistency, and caused her no physical discomfort except for bleeding on the slightest provocation. She consulted her family dentist, who referred her to a colleague for diagnosis and management. On June 12, 1957, an excisional biopsy was performed and the specimen was mailed to the Oral Pathology Laboratory at the School of Dentistry with a provisional diagnosis of malignant melanoma.

Grossly, the tumor measured 3 by 2 by 1 cm. and was dark in color. Unlike a blood clot, it was adherent to the overlying tissue. Microscopically, the specimen was composed of sheets of spindle-shaped cells which exhibited marked pleomorphism. The nuclei were large, of different size and shape, and tended to be hyperchromatic. Throughout the tissue was scattered pigment, both intracellularly and extracellularly. Moderate mitotic activity was observed. The overlying mucosa was intact and showed no evidence of junctional activity. However, examination of serial sections from the specimen demonstrated junctional activity similar to that seen in cutaneous melanoma arising from junctional nevi (Figs. 1 and 2).

The patient was admitted to the University Hospital on June 17, 1957. Her medical history and laboratory tests were noncontributory. Roentgenographic examination of the chest showed no evidence of pulmonary metastases. On physical examination, no palpable lymph nodes could be demonstrated.

Intraoral examination revealed the site of excisional biopsy, extending from the right central incisor to the distal side of the right second premolar on the buccal surface and

From the Divisions of Oral Pathology (A. P. C. and R. J. G.) and Oral Surgery (R. J. B.), School of Dentistry, University of Minnesota.

from the right lateral incisor to the second premolar on the lingual aspect. There was also pigmentation of the gingiva, which extended to the left premolar region (Fig. 3). Another biopsy specimen was procured from the pigmented area and showed absence of neoplastic cells. The patient and her family were informed of the serious nature of the

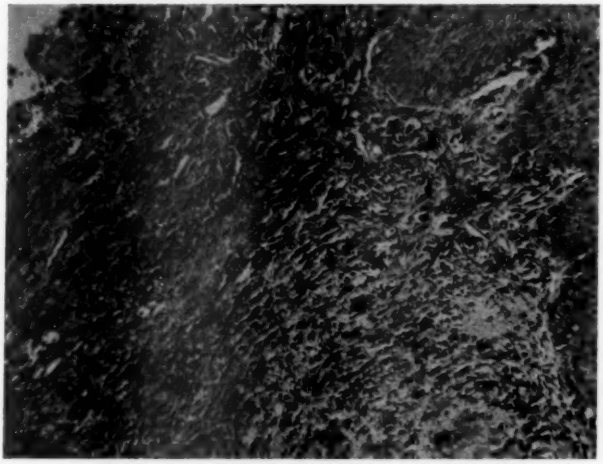


Fig. 1.—Photomicrograph (low magnification) showing cellularity of the tumor mass, distribution of melanin pigment, and junctional activity at the right-hand corner.

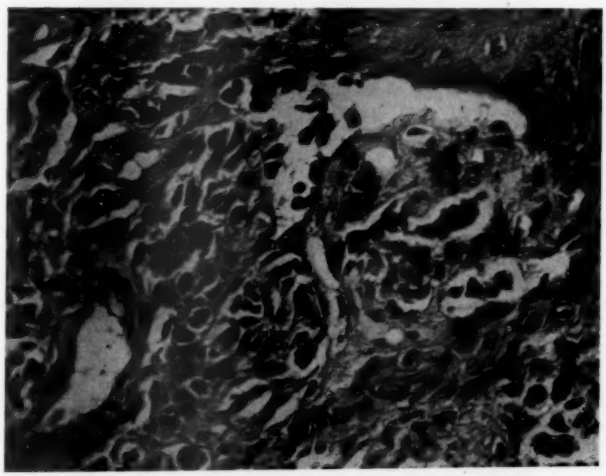


Fig. 2.—Photomicrograph (higher magnification) showing part of the section with junctional activity. Note that the basal-cell layer is unidentifiable. The neoplastic cells are pleomorphic and filled with melanin pigment.

disease and of the contemplated plan of treatment, which included radical maxillectomy. The patient refused treatment and was, therefore, discharged from the hospital. She was then followed by her dentists, who noted a lump under her right jaw on Aug. 31, 1957.

Subsequently, her whereabouts was not known for almost a year. On Aug. 19, 1958, she was taken to a local hospital in a semicomatose state. History could not be obtained at this time. She had no local recurrence but there was a 3 by 4 cm. mass at the angle

Fig. 3.—Photograph showing spread of melanin pigment of the gingiva on the side opposite the tumor mass.

Fig. 4.—Roentgenogram showing bilateral pulmonary metastases.

of the right mandible. There also was a positive bilateral Babinski reflex. The patient was treated with fluids, vitamins, and stimulants; she responded favorably and was discharged on Sept. 7, 1958. At the time of this hospitalization her chest films showed

lobulated masses in both lungs (Fig. 4). On September 20 the patient was readmitted with severe headache and progressive lethargy. Rapidly becoming unconscious, she developed pulmonary edema and died within twelve hours after admission. No autopsy was performed.

## DISCUSSION

Primary malignant melanoma of the oral cavity arises from melanoblasts. The presence of melanoblasts in the oral mucosa has been demonstrated by Laidlaw and Cahn[2] and Cattoni.[3] Cases of oral nevi have been reported by several other investigators.[4-6] Green and associates[7] have established three reliable criteria for primary malignant melanoma of the oral cavity: (1) the presence of a clinical and microscopic tumor in the oral mucosa; (2) the presence of intraepithelial activity in the lesion; and (3) inability to demonstrate any other primary site. The present case meets all three requirements and is, therefore, primary in the mouth. The neoplasm is twice as common in males as in females. Nearly 75 per cent of the reported cases are in patients over 40 years of age, with a peak occurring in the sixth decade. The neoplasm has been reported in all races. The site of predilection for malignant melanoma of the oral cavity is the maxilla, where more than 80 per cent of the tumors originate. The other sites of involvement, in their order of frequency, are the mandible, the cheeks, the tongue, the floor of the mouth, and the lips. In the maxilla, the hard palate, the alveolar ridge mucosa and the soft palate are involved in that order. The appearance of oral melanosis and the subsequent development of melanoma in the pigmented area are not uncommon. The neoplasm is usually dark brown to black in color, nonelevated or raised, and painless. When raised, it may be smooth or nodular and soft in consistency. Rarely, a malignant melanoma of the oral cavity is nonpigmented. Ulceration and bleeding are quite common. In advanced cases there may be destruction of underlying bone, with loosening and exfoliation of teeth. The neoplasm has a marked potentiality for regional as well as distant metastases. Occasionally, a swelling in the submandibular region caused by the spread of the disease to lymph nodes may be the initial symptom which would warrant medical attention. The tumor offers a much worse prognosis than cutaneous malignant melanoma. The five-year survival rate is less than 5 per cent. The treatment of choice is radical excision following early detection of the lesion. X-ray therapy does not hold any promise in the treatment of this tumor.

The cause of the high incidence of primary malignant melanoma in the maxilla needs further study. It is plausible that there is a quantitative difference in the activity of the melanoblasts in different parts of the oral cavity.

## SUMMARY

We have discussed in detail a case of malignant melanoma of the alveolar mucosa in a 64-year-old white woman who died of widespread metastases. The tumor had developed from a pre-existing pigmented patch which had been present for at least three years. The neoplasm was considered to have originated

in the oral mucosa, since it met three reliable criteria set up by Green and associates.[7] Finally, it has been suggested that the higher incidence of malignant melanoma in the maxilla could be due to the presence of an increased number of active melanoblasts at this site.

The authors are grateful to Drs. W. J. VonBank and G. F. Kuehner of New Ulm, Minnesota, for referring this patient to the School of Dentistry and also for keeping us informed concerning her medical status.

REFERENCES

1. Chaudhry, A. P., Hampel, A., and Gorlin, R. J.: Primary Malignant Melanoma of the Oral Cavity: A Review of 105 Cases, Cancer 11: 923, 1958.
2. Laidlaw, G. F., and Cahn, L. R.: Melanoblasts in the Gum, J. D. Res. 12: 534, 1932.
3. Cattoni, M.: Melanoblasts in the Inflamed Gingivae, ORAL SURG., ORAL MED. & ORAL PATH. 6: 1095, 1953.
4. Allen, R., and Bruce, K. W.: Nevus of the Gingivae, J. Oral Surg. 12: 257, 1954.
5. Couch, D. C., Jr.: Junctional Nevus of the Palate, J. Oral Surg. 14: 334, 1956.
6. Thoma, K. H.: Carcinoma, Sarcoma, and Melanoma; Their Diagnosis and Treatment, J. Oral Surg. 15: 50, 1957.
7. Green, G. W., Haynes, J. W., Dozier, M., Blumburg, J., and Bernier, J. L.: Primary Malignant Melanoma of the Oral Mucosa, ORAL SURG., ORAL MED. & ORAL PATH. 6: 1435, 1953.

# ENDODONTICS

*The American Association of Endodontists*

*Captain Warren J. Hedman, Editor*

. . . . . .

## ROOT CANAL TREATMENT WITH BACITRACIN-NEOMYCIN AS CAUSE OF FLARE-UP OF ALLERGIC ECZEMA

*Veikko Pirilä, M.D.,* and Aimo V. Rantanen, Odont. Lic.,***
*Helsinki, Finland*

### INTRODUCTION

THE use of antibiotic therapy in the various branches of medicine is widespread. A few of these antibiotic drugs have been applied in dentistry as well, although their value in local treatment is still under discussion.[4] Of many antibiotics tested bacteriologically and clinically, combinations containing bacitracin and/or neomycin (Bacimycin dentale, Grossman's PBSC paste, Nebacetin dental, and Neotrasin) have proved to be most suitable.[10, 12-14] Their favorable properties include a wide antibacterial spectrum, efficacy, ease of handling, and a low incidence of complications.[6, 12] In recent years the bacitracin-neomycin combination has become the most common medication in treatment of infected root canals in Finland. This combination, shown to be safe in many thousands of cases, is not absolutely without danger, however. A case of allergic reaction is reported here as a warning against the careless use of these antibiotics. It must also be remembered that this kind of reaction may be sudden and serious.

To date we have not seen in the literature reports of complications arising from dental use of bacitracin or neomycin. On the other hand, the sensitizing effect of these drugs when used topically on the skin or mucous membranes is already well known.[3, 5, 8]

### CASE REPORT

The patient, a 39-year-old man, had suffered for two days from a toothache. The tooth was tender, and there had been spontaneous pain during the night.

*Professor of Dermatology, University of Helsinki.
**Lecturer in Operative Dentistry, Institute of Dentistry, University of Helsinki.

The examination revealed tenderness of the right lateral incisor (2+), both vertically and horizontally. This tooth had been filled mesially and distally with filling porcelain cement and at the cingulum with silver amalgam. The obvious diagnosis was total pulpitis or pulp gangrene. It was decided to open the pulp chamber. After opening, a bad odor and yellowish pus, as well as a thinner hemorrhagic exudate, were noted. This confirmed the diagnosis of pulp gangrene in the right lateral incisor.

The pulp chamber and root canal were opened to the apex and cleaned by mechanical and chemical means. The canal was then filled with a paste of Neotrasin-Ringer's solution. Neotrasin "dentale" is composed of neomycin sulfate, 1.66 grams, and bacitracin, 3.33 grams. The canal was filled as completely as was possible by means of a Lentulo needle. To allow a free drainage, the cavity was closed with two cotton pellets.

After four hours the patient reported to the dentist that he was not feeling well and inquired about the drugs which had been used. Upon being informed that Neotrasin had been used in the treatment, he stated that he was allergic to some "mycins." The patient was requested to return immediately for removal of the Neotrasin from the root canal.

The patient reported severe toothache extending to the right cheek and stated that about one and one-half hours after the canal had been filled the palms of his hands had begun to itch. Thereafter erythema and swelling appeared on the face. He stated further that the day before he had taken aspirin for his toothache and that about two hours after the canal filling he had taken two Compral tablets (trichlorethanolurethan-dimethylaminophenyldimethylpyrazolone 0.5 gram) and two Distra Pamyl tablets (acetylsalicylic acid 0.5 gram and correctives).

On re-examination, sunburnlike redness and edema on the face were observed. There was severe universal itching which was most severe on the popliteal folds, the right forefinger, and the amputation stump of the left leg. In addition, the patient had difficulty in swallowing and breathing, and the pharynx and oral mucosa were inflamed.

The root canal was reopened and the Neotrasin was removed with care. The drug was removed with an aspirator in order to prevent its spreading to the inflamed mucous membranes. The drug was absorbed first with dry cotton by means of root canal needles and thereafter with concentrated hydrogen peroxide. In addition, the canal was enlarged mechanically with root canal reamers and files, after which it was thoroughly rinsed and cleaned chemically. The cavity was closed with two cotton pellets and the canal was left free.

Aggravation of the eczema, with oozing, occurred within the first twenty-four hours and a physician was consulted. Under cortisone and antihistamine treatment, the eczema cleared up in one week, leaving only slight eczematous changes on the amputation stump and on the right forefinger.

After two days the root canal was filled with gutta-percha points, resulting in slight overfilling at the apex, and recovery followed without other complications.

It seemed obvious that the allergic reaction had been caused by Neotrasin powder, since the patient already had been sensitized to bacitracin and neomycin (see below). To be sure of this, however, the possibility that analgesics taken by the patient had caused the reaction had to be excluded. Therefore, the patient was given two tablets of Compral and Pamyl; no harmful effects were observed.

Some years before, the patient had eczema on the amputation stump of his left leg and had treated it with Orion Bacimycin ointment (neomycin sulfate 0.005 gram, bacitracin 500 units ointment base ad 1.0 gram). This had resulted in a sensitization to bacitracin and neomycin which was substantiated by one of us (V. P.) with positive patch tests. After the use of this ointment had been discontinued, the eczema was alleviated except for an occasional recurrence on the right forefinger. At the time the patient had been advised to avoid medicaments containing these antibiotics. For two years he had done so, but about two weeks before the events reported above, he had inadvertently treated his pharyngitis with Tyrobacin throat tablets (bacitracin 200 units, tyrothricin 0.001 gram, benzocaine 0.005 gram) in a dosage of six tablets daily for two days. During this period the condition had

been considerably aggravated. Furthermore, the oral and lingual mucosa had become intensely inflamed and swelling of the lips as well as rhagades at the angles of the mouth had developed. The patient stopped using the tablets and was well in six days. As a result of this unpleasant experience, he decided to be more careful to avoid exposure to bacitracin and neomycin. In spite of this, he did not escape another unpleasant incident described above, which occurred in connection with tooth treatment.

The same patient was later given neomycin internally. As smaller doses did not produce a clear reaction, he was given two tablets (0.165 gram each) four times during one day, making a total of 1.3 grams. Daily doses five to ten times as high have been used for preoperative medication.[1, 2]

About six hours after the patient had taken the first two tablets, he had diarrhea but no other signs or symptoms. After twenty-four hours the skin on the popliteal folds began to itch, and a day later a follicular eczema had developed there and on the thighs and there was edema of the face. As there was no improvement on the third day, cortisone treatment was started.

This case shows that bacitracin in throat tablets and a bacitracin-neomycin combination used as a powder for root canal treatment can cause a flare-up of eczema in patients sensitized to these antibiotics. The overfilling demonstrates the access of the allergen from the root canal into the periapical focus. From there it was easily carried to the skin by the blood stream. Furthermore, it can be seen that, although neomycin is absorbed from the intestine in minimal quantities which have no systemic toxic effect, these small amounts suffice to produce eczematous reactions in sensitized skin.

## DISCUSSION

Since it was highly probable that the patient had an allergic reaction to a bacitracin-neomycin combination, the first task was to eliminate these drugs as completely as possible from the root canal and from the periapical tissues. The canal lumen, even a narrow one, can be cleaned, but it is almost impossible to remove traces of the drugs which have reached the periapical tissues. The removal of a tooth would remove all of the drug in the root canal and in the dental tissues, but this method would be likely to spread the allergen present in the perifocal tissues into the blood stream. Furthermore, the most conservative method which allows preservation of the natural tooth is always to be preferred.

On the other hand, after the drug has been removed from the root canal, it also may be possible to neutralize some part of the drug extended into the periapical area. Theoretically, there are several ways to neutralize the effects of organic compounds in dentinal canals, focus, and adjacent tissues. Oxidation was tried in this case. Reduction, heating, and destruction with strong acids or alkalis can be used. In addition, the concentration of an allergen can be reduced by appropriate solvents. Both bacitracin and neomycin are soluble in water.

In severe allergic and anaphylactic reactions, the first aid consists of intramuscular or intravenous administration of Adrenalin derivatives, soluble cortisone or ACTH compounds, or antihistamines. Prescription and administration of these therapeutic agents by dentists is not permitted in the Scandinavian

countries, and therefore the use of these drugs requires cooperation with a physician.[7, 11] In addition, even the milder cases often offer diagnostic difficulties.

As far as we know, the case described here is the first one reported to be due to the use of bacitracin-neomycin suspension in dental practice and consequently is to be considered a rarity. It reminds us, however, of the situation that arose when the first cases of allergic eczema which resulted from topical treatment with bacitracin and neomycin were described in 1949 and 1952, respectively. Up to 1955, very few cases had been reported. During recent years the number has increased markedly; in 1959 Pirilä and Rouhunkoski[9] reported a total of 184 cases of hypersensitivity to bacitracin and neomycin.

In the present case, the patient had been sensitized primarily to this combination through treatment of his eczema with an ointment containing these antibiotics. The use of similar drugs for medication of the root canal infection provoked a flare-up of the eczema. Since the number of cases of eczematous hypersensitivity to bacitracin and neomycin is increasing and the use of these antibiotics is becoming more and more common in dental practice, an increase in the incidence of this kind of reactions is to be expected. In the future, therefore, dentists may be confronted with such complications more often than in the past.

As these reactions may occur suddenly and be severe, and as their control often may be difficult, preventive measures are desirable. Before using preparations containing bacitracin and neomycin, the dentist should try to ascertain that the patient has not had allergic reactions to these antibiotics on his skin or mucous membranes. The taking of careful history is of primary importance. Skin testing is a method that is reliable only in the hands of a competent dermatologist. There is a great possibility of misinterpretation of the results, particularly as far as bacitracin and neomycin are concerned. Skin tests with these antibiotics tend to be positive only inconstantly, and the reactions appear late and are easily overlooked.

SUMMARY

A patient previously sensitized to bacitracin and neomycin as the result of topical treatment of eczema acquired a flare-up allergic reaction from local use of these antibiotics in root canal medication. The signs, which appeared in less than two hours, included strong and wide eczematous changes and an acute inflammation of oral and pharyngeal mucosa which interfered with swallowing and breathing. A similar reaction could be reprovoked by giving neomycin orally to the same patient.

Since the number of cases of eczematous hypersensitivity to bacitracin and neomycin is increasing, and since the use of these antibiotics is becoming more and more common in dental practice, an increase in the incidence of this kind of reaction is to be expected. The difficulties in detecting the actual allergen are pointed out, and some methods for treatment, including first-aid measures, and for prevention are suggested.

REFERENCES

1. Anlyan, William G., Hart, D., Georgiade, Nicholas G., and Poston, Mary A.: Intestinal Antisepsis With Oxytetracycline (Terramycin) and Neomycin, A. M. A. Arch. Surg. **68**: 28-32, 1954.
2. Davis, John H., Kuhn, Ludvig R., and Amspacher, William H.: Preoperative Preparation of the Bowel With Neomycin, Surgery **35**: 434-439, 1954.
3. Epstein, Stephan, and MacCormic, George I.: Conjunctivitis Due to Neomycin Sensitivity, A. M. A. Arch. Ophth. **60**: 1000-1002, 1958.
4. Grossman, L. I.: A Report on the Second International Conference on Endodontics, Internat. Dent. J. **9**: 382-393, 1959.
5. Hjorth, Niels: Overfølsomhed for Neomycin-Bacitracin-Salver, Ugesk. f. læger **120**: 1323-1327, 1958.
6. Council on Drugs, American Medical Association: New and Nonofficial Remedies, Philadelphia and Montreal, 1959, J. B. Lippincott Company.
7. Nordqvist, P.: Något om akuta kollapstillstånd i dental praxis, Sveriges tandl.-tidning. **51**: 173-181, 1959.
8. Pirilä, V., and Wallenius, T.: Über die Ekzematöse Sensibilisierung gegen Neomycin und Bacitracin, Hautarzt **8**: 518-519, 1957.
9. Pirilä, V., and Rouhunkoski, S.: On Sensitivity to Neomycin and Bacitracin, Acta dermat.-venereol. (In press).
10. Pohto, Mauri, and Parmala, Mauri: Medication of Root Canal Infections, Acta odontol. scandinav. **16**: 389-402, 1958.
11. Rantanen, Aimo V.: Lääkkeiden annostuksesta Pohjoismaissa hammaslääkärin kannalta (On Prescription Rights in Dentistry in the Northern Countries, With an English summary), Suom. hammaslääk. toim. **55**: 70-77, 1959.
12. Rubbo, Sydney D., Reich, Julien, and Dixson, Shirley: The Use of a Combination of Neomycin, Bacitracin and Polymyxin in Endodontia, ORAL SURG., ORAL MED. & ORAL PATH. **11**: 878-896, 1958.
13. Søndergaard, Onse: Klinisk-bakteriologiske undersøkelser over anvendelsen af Nebacetin i rodkanalbehandlingen, Tandlaegebladet **60**: 140-157, 1956.
14. Wolfsohn, Bertram L.: Effectiveness of a Group of Endodontic Therapeutic Agents, ORAL SURG., ORAL MED. & ORAL PATH. **11**: 1394-1403, 1958.

ISO ROOBERTINKATU 13 (DR. PIRILÄ).
YRJÖNKATU 38 (DR. RANTANEN).

# TOPICAL USE OF CORTICOSTEROIDS FOR THE RELIEF OF PAIN SENSITIVITY OF DENTINE AND PULP

*Arthur E. Fry, D.D.S.,* Robert F. Watkins, D.M.D.,** and Nilkanth M. Phatak, Ph.D.,*** Portland, Ore.*

DEEP penetration of caries into the dentine or the extension of caries to the pulp chamber, as well as trauma from restorative procedures on vital teeth, produces a definite pain hypersensitivity of the exposed dentine and of the hyperemic pulp. The normal inflammatory pulpal response increases the capillary permeability and allows fluid and cells to escape into the surrounding tissues. There is a rise of intervascular pressure in the pulp chamber which may extend to the apex of the root and stop the vascular flow or occlude the vessels at their site of entry or exit at the apical foramen. This basic tissue reaction to the stress of caries or to the trauma of restorative procedures resolves itself in time, as adaptation succeeds, or it ends in a variety of degenerative and repair sequelae.

The dentinal tubules are permeable to many substances. Molecules of chemical agents, such as soluble corticosteroids, when applied to the exposed dentine, diffuse through the dentinal tubules into the pulp chamber. In contact with the pulpal tissue, the corticosteroids exert their sedative, anti-inflammatory effect. Depression of the normal or operatively induced hyperemic inflammatory reaction can be expected to suppress pain hypersensitivity of exposed dentine and pulp.

## MATERIALS AND METHOD

Patients of both sexes, varying in age from 5 to 67 years, were included in the study without regard to age, sex, duration or nature of pain, or evaluated findings of physical condition or medical history. All of these patients were either undergoing routine treatments in the student clinics or reporting to the diagnostic clinic for emergency treatment for relief of dental pain. No attempt was made to establish an aseptic technique by using a rubber dam. Cotton rolls and a saliva ejector were used to isolate the area so as to minimize contamination of the field. The medication consisted of a small drop of camphorated para-

From the Department of Oral Diagnosis, University of Oregon Dental School.
*Associate Professor and Head of Department of Oral Diagnosis.
**Assistant Professor of Dentistry, in charge of Endodontics.
***Professor of Pharmacology and Head of Department of Pharmacology.

chlorophenol with metacresyl acetate to which was added enough Meticortelone powder* to form a thin paste.

Those cases in which pulpal hyperemia occurred as a result of restorative interference were treated as follows:

1. When a full crown preparation was involved, the prepared medication was initially applied to the exposed dentine, after which a temporary crown was cemented with zinc oxide and eugenol. In restorative procedures involving inlay or gold foil restorations where traumatic pulpal hyperemia had occurred, the restorative material was removed, medication was applied and the cavity was sealed with zinc oxide and eugenol, followed by zinc oxyphosphate cement.

2. When a vital operative pulpal exposure had occurred under aseptic conditions, the Meticortelone paste was picked up on a small pellet of cotton and placed directly over the exposure to protect the pulp. A thin mix of zinc oxide and eugenol was then placed over this without pressure. Occasionally this treatment was modified by placing an autoclaved asbestos disk or cigarette paper over the medication, after which the zinc oxide and eugenol was placed and the cavity was sealed with zinc oxyphosphate cement.

3. When emergency clinic patients reported with dental pain and x-ray films indicated the possibility of pulpal exposure if carious dentine were completely removed, the Meticortelone paste was placed, after partial removal of caries, over the unexcavated carious dentine. This was covered w h zinc oxide and eugenol, and the seal was completed with zinc oxyphosphate cement. In those teeth with only an occlusal involvement, the cavity was sealed in addition with an amalgam restoration. If the proximal surfaces were involved, a stainless steel band was placed around the tooth to ensure retention of the restorative materials.

## RESULTS

All patients treated in our clinics by this method stated that their pain hypersensitivity had subsided promptly. When the patients were queried after twenty-four hours, either on their return to the clinics or by telephone, pain was absent in the large majority of cases. If pain still existed, the patient was requested to report for re-evaluation and retreatment. This retreatment invariably obtunded pain hypersensitivity, and thereafter the patient remained comfortable and free of pain. The elapsed time between the initial treatment with Meticortelone paste and the recheck varied from four to six weeks. On recall examination, vitality tests were made and x-ray films were obtained. All treated teeth responded normally to vitality tests. All patients were free of symptoms and showed x-ray evidence of calcification or secondary dentine formation. In three patients this could also be verified by clinical observation. Two of

*Meticortelone powder, a brand of prednisolone soluble, is a product of the Schering Corporation, Bloomfield, New Jersey.

these patients had lost the restorative material two weeks before the recall examination, and the third had lost it three to four days prior to the examination. These patients stated that the treated teeth were no longer sensitive, and examination with mouth mirror and explorer disclosed formation of a hardened dentinal layer. In those cavities involving proximal surfaces or incisal angles, we propose to use stainless steel bands to prevent loss of treatment material. Ten weeks after the initial treatment each patient will be re-evaluated to determine the advisability of placing a more permanent type of restorative material. In this series of cases we encountered one failure. The patient was a 51-year-old woman who had an alloy restoration placed in her tooth on Feb. 27, 1959. It became deficient and was replaced with an inlay restoration in the student clinic. This, too, proved to be deficient and was replaced on May 15, 1959. The patient remained symptom-free until July 3, 1959, when she reported to the diagnostic emergency clinic with a severe toothache. She was then treated with the Meticortelone paste, and the pain promptly subsided. The patient reported that she was free of pain on July 4, but she felt the toothache again on July 5, 6, and 7, when it became unbearable, and she needed treatment for its relief. Under the circumstances, it was decided that the tooth should be extracted rather than retreated and retraumatized. Sectioning and histopathologic examination of the extracted tooth should indicate the existing pulpal damage and the degree of its remaining reparative potential.

## DISCUSSION

Prior to the introduction of our proposed therapeutic approach, cases of pulpal hyperemia and exposure were treated with rather limited success. Diverse agents were recommended and used.[1, 2] Such conditions as youth and good health, absence of caries around the exposure, little or no bleeding and laceration of the pulp, and no previous history of pain were some of the stringent criteria recommended for the proper selection of cases for a successful outcome. Our recommended treatment is based upon the highly selective and anti-inflammatory topical effects of the corticosteroid, Meticortelone, synergistic with the soothing, antiseptic, and regenerative action of camphorated parachlorophenol with metacresyl acetate. We wish to emphasize that the procedures used and the results obtained thus far represent only a preliminary clinical appraisal. The findings substantiate our hypothesis and indicate the basic potential of the corticosteroids and related drugs in previously untreatable teeth, from the standpoint of conservation of pulp vitality. Most of the teeth that received this particular therapy would have been treated in its absence by either endodontic procedures or extraction.

## SUMMARY AND CONCLUSIONS

Forty-three teeth with either pulpal exposure or carious invasion were studied and treated topically with a corticosteroid (Meticortelone) and camphorated parachlorophenol with metacresyl acetate paste. Clinical evaluation of subjective and objective signs and symptoms, as well as data on vitality

tests and x-ray film evidence, was obtained for more than four months. To date, only one of the treated teeth in this group has had to be extracted. The other teeth have remained pain-free and functionally useful. These data substantiate and strongly indicate the high potential of the topical use of Meticortelone for the relief of dentinal and pulpal pain hypersensitivity and for conserving the vitality of exposed dentine and pulp tissue.

REFERENCES

1. Schmidt, H. S., and Burkman, N. W.: Cavity Medication, D. Clin. North America, pp. 165-176, March, 1958.
2. Nyborg, Hilding: Capping of the Pulp; the Processes Involved and Their Outcome, Odontol. Tidskr. 66: 293-362, 1958.

## RESEARCH

# PAROTID GLAND HETEROTRANSPLANTS AND SHOPE PAPILLOMA VIRUS

*Harold S. Fleming, D.M.D., M.Sc., D.Sc., Washington, D. C.*

### INTRODUCTION

SALIVARY gland disease of viral origin exists in man and lower animals.[2] Strains of species-specific viruses can produce salivary gland disease in experimental animals, such as mice and guinea pigs.[8, 10] Species-susceptible tooth germs were altered in their expected growth and development when treated with Shope papilloma virus before transplantation.[4] It was also found that the behavior of these tooth germ transfers under such conditions was analogous to their behavior when transplanted with chemical carcinogens, such as methylcholanthrene or dibenzanthracene. The effect of a species-specific virus on salivary gland transplants has not been heretofore reported. Susceptibility of parotid gland transfers to an infectious agent, such as the Shope papilloma virus, is important, since it may give some information on the many spontaneous salivary gland diseases of viral origin.

### MATERIALS AND METHODS

Fragments of glycerinated papillomas obtained from cottontail rabbits were washed several times with normal saline. Afterward, they were ground in a mortar or homogenizer, diluted with ten parts saline, and allowed to stand until any remaining fragments settled. The clear liquid was decanted and then passed through a Berkefeld candle filter. This was used to receive the parotid gland tissue before transplantation.

Parotid glands obtained from neonatal Dutch rabbits (immediately after birth) and late-term guinea pigs (65 to 70 day) were cut into small pieces and allowed to soak in this clear fluid for one-half hour. The glands were then transplanted to the subcutaneous spaces of Syrian hamsters.

The animals were sacrificed intermittently, by chloroform, between the eighth and forty-sixth days following transplantation. Recovered transplants were fixed in formalin, sectioned, and stained with hematoxylin and eosin.

From Howard University College of Dentistry, Department of Research.

Transplants were made to the subcutaneous spaces of hamsters as follows (Table I):

1. 104 hosts received rabbit parotid gland transfers in which Shope papilloma virus was used.

2. 29 hosts received late-term guinea pig parotid glands in which Shope papilloma virus was used as the infectious agent.

3. 21 hosts received untreated rabbit parotid gland transfers. Immediately after removal, the parotid gland tissue was washed in saline and put into the refrigerator for about fifteen to twenty minutes. The tissue was then cut into small pieces that could easily be drawn up into a No. 16 or No. 18 transplantation trocar. The pieces of gland tissue were then put into the Shope extract and back into the refrigerator for approximately thirty minutes. These tissues, if kept at room temperature, rapidly became sticky and very hard to handle. Thus the foregoing procedure was followed.

TABLE I

| HOSTS | SURVIVORS* | TISSUE SOURCE | TISSUE TREATMENT | TISSUE RECOVERED |
|---|---|---|---|---|
| 104 | 81 | Neonatal Dutch rabbits | Shope papilloma virus | 47 |
| 29 | 22 | 65- to 70-day guinea pigs | Shope papilloma virus | 16 |
| 21 | 19 | Neonatal Dutch rabbit | None | 15 |

*A number of the animals were lost or were found dead in the cages and discarded.

Fig. 1 shows a section of rabbit parotid gland before transplantation. Parotid glands survived transfer up to and beyond the limit of the present experiments, which was forty-six days. An untreated transfer, thirty-two days following transplantation, is shown in Fig. 2. Growth and development of untreated gland tissue can be determined by comparing Figs. 1 and 2.

Following exposure to the virus, parotid gland transplants exhibited the histologic alterations depicted in Figs. 3, 4, 6, 7, and 8. Similarly treated guinea pig parotid glands failed to manifest the same changes. A section of guinea pig transplant recovered after twenty-two days in a hamster is shown in Fig. 5.

Soon after transplantation, papillomatous proliferations were apparent where rabbit parotid glands were exposed to the Shope papilloma virus before transplantation (Fig. 3). Papillomatous proliferations were not obtained with transplants of guinea pig parotid glands. Neonatal rabbit parotid glands untreated before transplantation have a different appearance as shown in Fig. 2.

Neonatal parotid glands that were treated with the Shope papilloma extract showed a general pattern of degeneration in certain areas and increased mitotic activity in other groups of acinar cells. In some places there was an acute inflammatory reaction with much necrosis, while in other areas there was a generalized chronic inflammatory reaction. In these latter instances, numbers of plasma cells, eosinophilic granulocytes, and multinucleated giant cells were

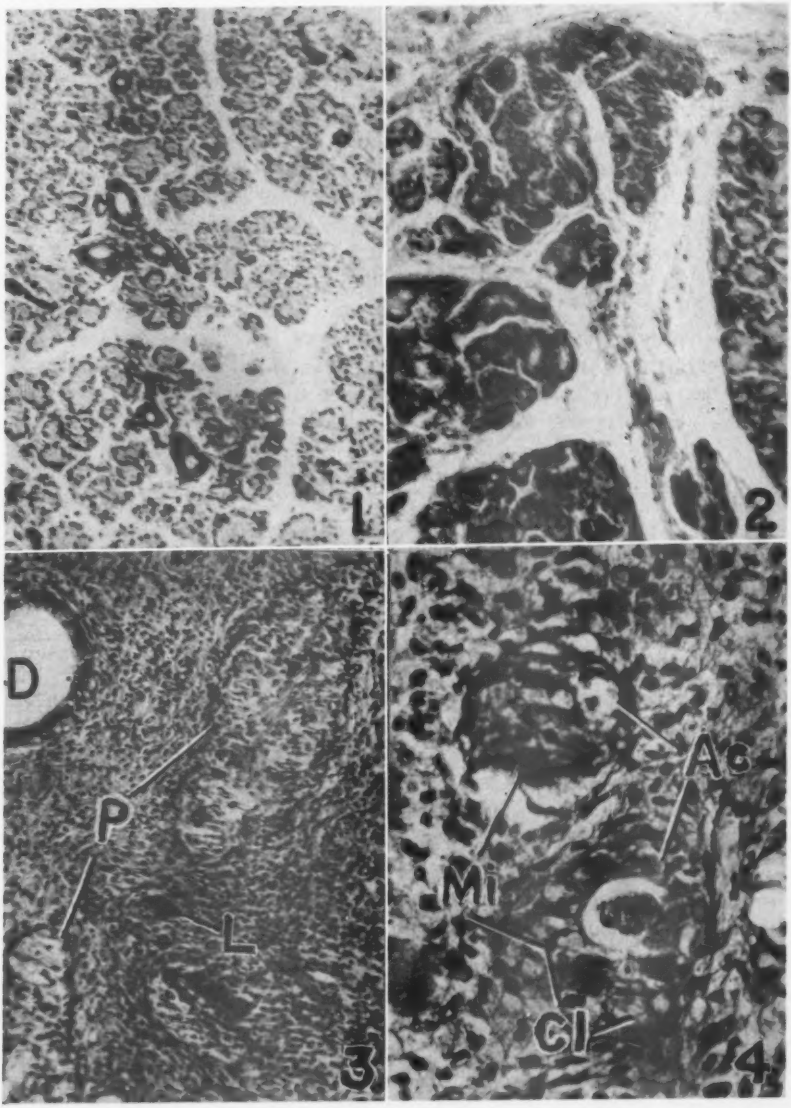



**Fig. 1.**—Neonatal rabbit parotid gland. (Original magnification, ×270; reduced 1/6.)

**Fig. 2.**—Untreated neonatal rabbit parotid gland after thirty-two days in a hamster subcutaneous space. (Original magnification, ×270; reduced 1/6.)

**Fig. 3.**—Shope-papilloma-treated neonatal rabbit parotid gland after eight days in the subcutaneous space of a hamster. (Original magnification, ×265; reduced 1/6.)

**Fig. 4.**—Shope-papilloma-treated neonatal rabbit parotid gland after eleven days in the subcutaneous space of a hamster. (Original magnification, ×1035; reduced 1/6.)

Key to Symbols:

*Ac* = Acinary cell groups.
*BV* = Blood vessel.
*CI* = Cytoplasmic inclusion.
*D* = Duct.
*K* = Keratin.
*L* = Langhan giant cell.
*Mi* = Mitotic figures.
*P* = Papilloma.

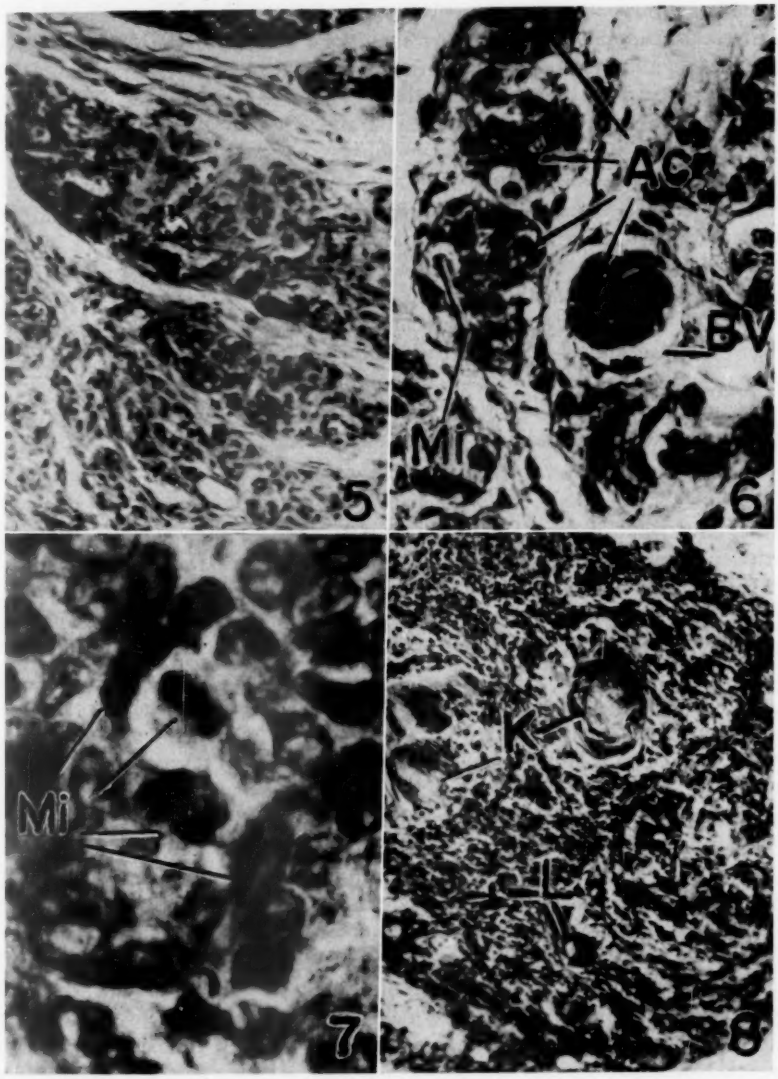



Fig. 5.—Seventy-day guinea pig parotid gland treated with an extract of Shope papilloma virus and transplanted to the subcutaneous space of a hamster for twenty-two days. (Original magnification, ×280; reduced ⅙.)

Fig. 6.—Neonatal Shope-treated rabbit parotid gland after forty-three days in subcutaneous space of a hamster. (Original magnification, ×1260; reduced ⅙.)

Fig. 7.—Higher magnification of a deeper cut of Fig. 6 to show mitotic figures. (Original magnification, ×2,900; reduced ⅙.)

Fig. 8.—Neonatal Shope-treated rabbit parotid gland after forty-three days in subcutaneous space of a hamster. (Original magnification, ×272; reduced ⅙.)

found. Lumina of acinar groups usually had debris, as shown in Fig. 4. Many cells had cytoplasmic inclusions that pushed the nucleus to one side. These cells were considerably distorted by inclusions that gave the nuclei a bizarre appearance. Many of these cells with odd-shaped nuclei, as well as other cells, were seen in various phases of mitotic division. Mitotic figures observed soon after transplantation are shown in Fig. 4, and later stages are depicted in Figs. 6 and 7.

Later the bizarre appearance of the acinar groups of cells became lessened, but their increased size remained evident and some ducts were completely obliterated. Mitotic activity was still above normal, as shown in Figs. 6 and 7. Frequently, over these longer periods of the experiments, nests of dark-staining cells were observed, sometimes within vessels close to or associated with these transfers (Fig. 6). Also, over the longer periods of these experiments, nests of keratin were observed only occasionally. When this occurred, numbers of Langhans' giant cells within the surrounding stroma were observed (Fig. 8). These giant cells were also apparent when papillomatous proliferations were evident, as shown in Fig. 3.

## DISCUSSION

In these experiments, results differed from those attained previously with tooth germ transplants and the Shope papilloma virus.[4] It was found, however, as Greene[5-7] had determined, that following treatment with the Shope papilloma virus tissue transplants behaved in a species-specific manner. Thus, susceptibility to this infectious agent resided with the transfers and not with the hosts.

The abundant papillary proliferations and keratin formations that had been observed with the anlagen of rabbit teeth[4] were not observed with rabbit parotid gland transplants. In the previous experiments with tooth germs, most ameloblasts degenerated. From the outer enamel epithelium, however, papillary proliferations and keratin formations became evident. An interesting phenomenon was that certain cells among the ameloblasts were mitotically active. In the present experiments larger cell groups survived, but there were likewise larger areas of necrosis. Presumably, where acinar groups were most active, degenerative changes were more rapid and complete. This would coincide with the fate of enamel-secreting cells, as observed in the previous experiments. When degeneration was not evident, the cytologic picture showed greatly enlarged acinar cells with cytoplasmic inclusions and bizarre nuclei. Many of the cells in the surviving groups were at various stages of mitosis. This concurs with the fact that viruses are associated with salivary gland disease and the presence of intranuclear and cytoplasmic inclusions is considered pathognomic.[1-3, 8-10]

It has also been noted that salivary gland disease of viral origin results from species-specific viruses.[1, 8, 10] Since Shope papilloma virus is species specific, this would presumably account for the failure of guinea pig parotid gland transplants to behave like those of rabbit parotid glands.

Of particular interest were certain groups of the acinar epithelial cells during the latter stages of the present experiments. These nests of cells were observed near or within small vessels adjacent to lobes of the gland explants. Many of the cells were in mitotic division. These cell groups stained heavily with hematoxylin; this was at variance with the other adjacent areas of gland tissue. Bauer and Nicholas,[1] in their experiments with the salivary gland virus, observed that there were no inclusion bodies in the cells that they considered neoplastic. These dark-staining cells did not contain any inclusions in the present study, but they could not be considered malignant even though several of the criteria were met.

## SUMMARY

Exposure to the Shope papilloma virus altered the expected growth and development of neonatal rabbit parotid gland heterotransplants. Papillomatous proliferations were evident soon after transplantation. However, they were not as extensive and did not persist in the same manner, with abundant keratin formations, as those previously obtained with this virus and tooth germ transplants. Late-term guinea pig parotid gland transplants did not exhibit the same changes when treated with this virus. During the later stages of these experiments, nests of darkly staining cells were observed. Mitotic division was above normal, and at times these cell groups appeared to be within small associated vessels.

## CONCLUSIONS

1. Exposure to extracts of Shope papillomas altered the growth and development of neonatal rabbit parotid gland transplants.

2. Papillomatous proliferations of transplanted parotid gland tissue were evident in early transplants but were not found during the later stages of transplantation.

3. Transplants of near-term guinea pig parotid glands, when similarly treated before transplantation, were not susceptible to this virus.

4. Cytoplasmic inclusions, bizarre mitotic forms, and increased mitoses were observed in certain places in groups of acinar cells treated with Shope papilloma virus before transplantation.

5. Large necrotic areas were adjacent to surviving gland tissue. Nests of acinar cells were frequently observed in vessels during the later stages of these experiments.

6. At late stages of transplantation, only occasional nests of keratin were found.

## REFERENCES

1. Bauer, W. H., and Nicholas, G. G.: Interaction of a Salivary Gland Virus and Experimentally Produced Carcinomas of the Mouse Salivary Gland, Cancer Res. 14: 768-773, 1954.

2. Cappell, D. G., and McFarlane, M. N.: Inclusion Bodies (Protozoon-Like Cells) in the Organs of Infants, J. Path. & Bact. 50: 385-398, 1947.
3. Dewey, M. M.: A Histochemical and Biochemical Study of the Parotid Gland in Normal Hypophysectomized Rats, Am. J. Anat. 102: 243-273, 1958.
4. Fleming, H. S.: Shope Papilloma Virus and Tooth Germ Transplants, ORAL SURG., ORAL MED. & ORAL PATH. 11: 549-557, 1958.
5. Greene, H. S. N.: The Induction of the Shope Papilloma in Transplants of Embryonic Rabbit Skin, Cancer Res. 13: 58-63, 1953.
6. Greene, H. S. N.: Infectiousness of the Virus in Shope Papillomas Induced or Grown in the Variant Rabbit Strain and in a Resistant Species, Cancer Res. 14: 463-467, 1954.
7. Greene, H. S. N.: The Response of Skin From Rabbits Immune to the Shope Virus After In Vitro Infection and Transplantation to Normal Animals, Cancer Res. 15: 124-127, 1955.
8. Rivers, T. M.: Generalized Salivary-Gland Virus Infection. In Rivers, T. M. (editor): Viral and Rickettsial Infections of Man, ed. 2, Philadelphia, 1952, J. B. Lippincott Company, pp. 674-675.
9. Smith, M. G., and Vellios, F.: Inclusion Disease or Generalized Salivary Gland Virus Infection, Arch. Path. 50: 862-884, 1950.
10. Stewart, S. E.: Neoplasms in Mice Inoculated With Cell-Free Extracts or Filtrates of Leukemic Mouse Tissues. I. Neoplasms of the Parotid and Adrenal Glands, J. Nat. Cancer Inst. 15: 1391-1415, 1954-1955.

# HISTOLOGIC CHANGES PRODUCED BY PRESSURE INJECTION OF WHOLE BLOOD INTO THE INTERMEDULLARY SPACES OF DOG MANDIBLES

*Philip J. Holton, D.D.S., M.S., Providence, R. I.*

## INTRODUCTION

THE solitary cystic lesion found in the jaws of children and young adults has been called by a variety of names. The terms "simple bone cyst,"[1] "traumatic cyst,"[2] and "traumatic hemorrhagic cyst"[3] are used almost interchangeably in the dental literature. For the sake of consistency, the term "hemorrhagic cyst" will be used in this report. Many authors believe that the mandibular lesions are similar to the lesions found in the metaphysial region of the long bone. These lesions are commonly referred to as "unicameral cysts,"[4] "solitary cysts,"[5] and localized "osteitis fibrosa."[6]

Large series of cases of simple bone cysts have been reported by Coley,[7] Geschickter and Copeland,[8] and Jaffe and Lichtenstein.[9] Unfortunately, the jaws are not mentioned in these series. Lucas[10] is credited with reporting the first case of a hemorrhagic cyst in the jaws. Blum,[11] Rushton,[12] Olech and associates,[13] and Whinery[14] have reported or reviewed the majority of cases involving hemorrhagic cyst of the mandible.

Most of the theories regarding the pathogenesis of the lesion refer to the lesion found in the long bones. These theories have long been a matter of controversy.

Geschickter and Copeland[15] claim that the solitary cyst of the long bones is a healing form of localized osteitis fibrosa or benign giant-cell tumor. Monckeberg[16] and Konjetzny[17] were the first to develop this theory. Rushton[12] and Thoma[18] appear to have adopted this concept for the lesions found in the mandible.

Jaffe[19] believes the solitary cyst of the jaws to be a result of "an aberration in the development and growth of local osseous tissue." This theory was first conceived by Mikulicz,[20] who called the lesion "osteodystrophia cystica juvenilis." Mikulicz suggests trauma as the predisposing factor of the lesion.

Boetticher[21] and Beneke[22] were the first to conceive the theory of the "traumatic hematocyst" as related to the long bones. This theory was firmly

This investigation was supported by a fellowship (DF-6916) from the National Institute of Dental Research, United States Public Health Service.

This paper is an abridgment of a thesis presented to the Graduate School of Georgetown University, Washington, D. C., as partial fulfillment of the requirements for the degree of Master of Science in Oral Surgery.

supported by an exhaustive histologic study by Pommer[23] of a clinical case reported by von Haberer. Blum,[11] who reported the first cases of solitary bone cyst in the mandible, and Olech and colleagues[13] also appear to favor the theory of Boetticher[21] and Beneke.[22]

The above-named authors believe that an intermedullary hematoma is formed as a result of trauma. This trauma must not be of such force as to disrupt the continuity of the bone involved. Olech and his co-workers[13] believe that in most cases the hematoma will organize and heal by the formation of connective tissue with or without bone formation. However, if there is a failure of early organization and subsequent liquefaction, a hemorrhagic cyst will eventually form. The failure of organization is probably caused by the widespread hemorrhage into the red marrow with fragile sinusoids causing necrosis of the bony trabeculae in the area. Removal of the necrotic trabeculae is retarded because of the lack of fibrous connective tissue in contact with the traumatic focus. Osteoclasts become differentiated on the opposite surface of the trabeculae and thus remove the necrotic bone by undermining resorption. If, by the time the necrotic bone is removed, the clot becomes liquefied, then organization is impossible and a cyst forms. Expansion of the area is a result of infiltrating edema caused by the restriction of venous drainage.

The pathogenesis of the traumatic hemorrhagic cyst of the mandible is still rather controversial. In fact, Bernier[1] and Waldron[24] believe that no one particular etiological factor is responsible for the lesion. However, the hemorrhagic theory of Pommer,[23] which is supported by Blum[11] and by Olech and associates,[13] appears to have been more widely accepted.

In an attempt to substantiate the hematogenous theory of the formation of a hemorrhagic cyst, an experimental attempt was made to create an intermedullary hematoma by forcibly injecting whole autogenous blood into the intermedullary spaces of the mandibles of young dogs.

## METHOD

Seven dogs, six male and one female, were used in this experiment. The weights of the animals varied from 18 to 34 pounds.

The dogs were anesthetized with intravenous pentobarbital sodium. They were prepared and draped in the usual manner. An intraoral incision, 10 mm. in length, was made vertically through the mucoperiosteum in the bifurcation of the roots of the first permanent right mandibular molar, and another vertical incision was made between the second and third right mandibular molars. The mucoperiosteal flap was retracted to expose the cortical plate in these areas. The base of the flap was in the buccal gutter.

The cortical plate was punctured with a No. 8 round burr mounted on a dental handpiece. A 13 gauge needle was mounted on a 5 c.c. Sana-Loc control syringe and forced through the drill hole into the intermedullary space. The syringe was removed, leaving the needle firmly in place. Five cubic centimeters of whole blood was withdrawn from the previous venipuncture site in the cephalic vein. Under hand pressure, as much whole blood as possible

was forced in thirty seconds into the intermedullary space in each area. The needle and syringe were removed, and bone wax was placed in the puncture hole of the cortical plate to maintain as much pressure as possible. Finger pressure was maintained over this area while the second site of the mandible was injected in the same manner.

The areas were débrided of excess bone wax, and the mucoperiosteal flap was closed with two interrupted 0000 black silk sutures.

The animals were sacrificed by exsanguination at the following intervals: one dog at two days, 2 dogs at ten days, two dogs at twenty-one days, and two dogs at twenty-eight days. The mandibles were removed and placed in a fixing solution of 10 per cent formalin for forty-eight hours. A 15 mm. section of the injected area was cut and placed in a decalcifying solution. When the sections were decalcified, they were mounted in paraffin blocks, and sections from various areas of the block were stained with hematoxylin and eosin. A 10 mm. section in the region of the mandibular third molar of the left mandible was decalcified, sectioned, and stained as a control.

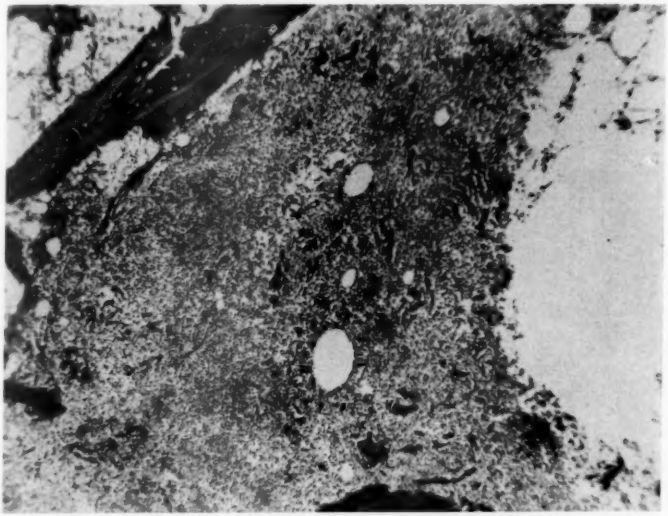


Fig. 1.—Note the debris and inflammatory elements scattered throughout the hemorrhagic area of the two-day dog. (Magnification, ×80; reduced ¼.)

## HISTOLOGIC RESULTS

*Two-Day Dog.*—Red blood cells were scattered throughout the marrow spaces. Also present were areas of frank hemorrhage which contained basophilic debris and acute inflammatory cells (Fig. 1).

*Ten-Day Dogs.*—The intermedullary bone was fairly active, as demonstrated by the osteoblasts lining the marrow spaces. Fibrous tissue proliferation and

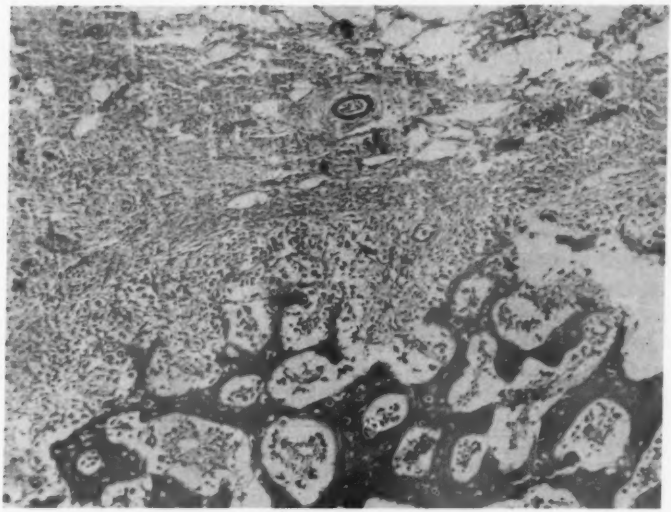


Fig. 2.—Note fibrous tissue proliferation (above) and new osteophytic bone (below) in one of the ten-day dogs. (Magnification, ×100; reduced ⅛.)

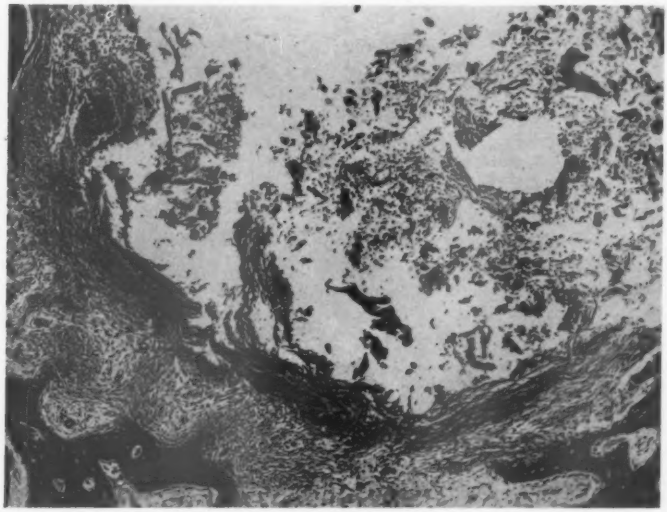


Fig. 3.—Note debris and inflammatory elements being walled off by dense fibrous tissue in one of the three-week dogs. (Magnification, ×63; reduced ⅛.)

a moderate infiltration of inflammatory elements were noted in the area of the burr hole (Fig. 2). New bone formation was evident in the deeper parts of the burr holes.

*Three-Week Dogs.*—The burr hole areas exhibited a small amount of debris and inflammatory elements. These areas were gradually filling in with loose and dense fibrous tissue. At the bottom of these areas the proliferating fibrous tissue was rather dense, and behind this were areas of new bone formation (Fig. 3).

*Four-Week Dogs.*—The areas of the burr holes were completely filled in with fibrous tissue. This fibrous tissue appeared denser than that seen in the previous dogs. Spicules of new bone lined with osteoblasts were noted along the sides as well as at the bottom of the burr holes (Fig. 4).

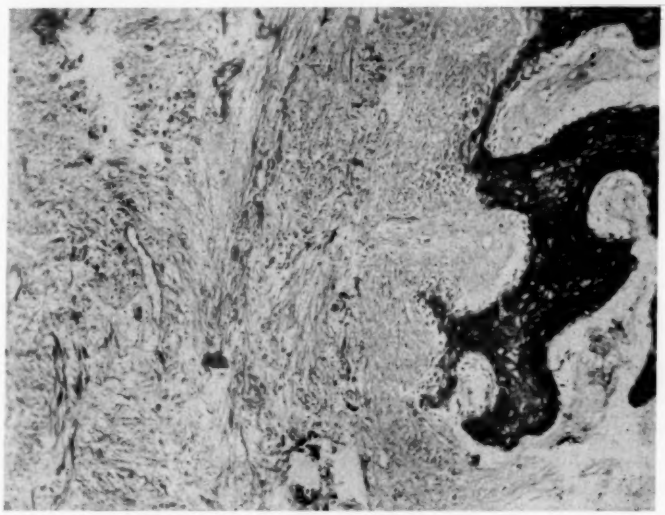


Fig. 4.—Note loose and dense fibrous tissue (left) and new bony spicules (right) in one of the four-week dogs. (Magnification, ×100; reduced ⅙.)

## DISCUSSION

The immediate response to the injection of whole antogenous blood into the intermedullary spaces of dog mandibles appeared to be an acute inflammatory reaction. This was exhibited in the two-day dog by the abundance of acute inflammatory cells in the area of hemorrhage. The hemorrhage area consisted of red blood cells of varying sizes. It was possible that the larger ones, which appeared to be undergoing hemolysis, were the ones that were injected and that the smaller ones, more natural-appearing red blood cells were a result of the hemorrhage that occurred when the hole was made in the cortical plate. However, this was purely a matter of conjecture. The bony fragments, which appeared as basophilic-staining particles, also resulted from the drilling of a

hole in the cortical plate. The bony fragments were also responsible for the inflammatory reaction.

The reaction in the ten-day dogs appeared to be one of organization. This was evidenced by the almost complete lack of red blood cells in the tissue spaces. Red blood cells were present only in the blood vessels. The gross hemorrhage apparently had been resorbed. The inflammatory cells were not as abundant as those seen in the two-day dog and were more chronic than acute. The debris present in the area of the burr hole was not so great. The first stage of healing was noted in the ten-day dogs. Loose fibrous tissue proliferation was noted. It apparently was attempting to wall off the debris in the region of the burr hole. Deeper in the burr hole was an area of new bone formation. Some of the sections also exhibited new bone formation on the opposite periosteal surface. This was, in all probability, compensating for the bone loss in the region of the burr hole. One section showed undermining resorption on one side of a spicule of old intermedullary bone and new osteophytic bone formation on the opposite side. This spicule was located at the bottom of the burr hole.

The reaction exhibited by the three-week dogs appeared to be a more advanced stage of healing. This reaction was confined to the area of the burr hole or the tissue in the immediate vicinity. No areas of hemorrhage were noted. A few scattered red blood cells were seen, but most of them were contained in engorged blood vessels. Inflammatory cells were very few in number, if present at all, in some sections. The fibrous tissue appeared more organized and was rather dense in some areas. It was making a better attempt to fill in or line the burr hole. Deeper and along the side of the burr hole, a greater amount of newly formed bone was noted than was seen in the previous dogs. In one of the three-week dogs, which exhibited the large radiolucent area in the radiograph and the large eroded area grossly in the anterior region, this area on the cortical plate was completely filled in with dense fibrous tissue which looked as if it were being replaced by new periosteal bone along one side.

The reaction exhibited in the four-week dogs was not much different from that exhibited in the three-week dogs. The difference was one of degree. The scattered red blood cells and inflammatory elements were few in number. The amount of debris seemed considerably less than that seen in the previous dogs. The fibrous tissue was denser and had filled in more of the burr hole. The new bone was more abundant and appeared to line the sides as well as the bottom of the burr hole. Some of the sections showed the new bone forming on the endosteal side of the buccal cortical plate for a considerable distance. This was probably compensating for the bone loss in the burr hole. The area of fibrous tissue that exhibited two cystlike areas was probably an area surrounding a spicule of old bone or debris that had been resorbed or washed out of the section. It appeared to be lined with two or three layers of fibroblasts.

## CONCLUSIONS AND SUMMARY

After evaluating the microscopic result of forcible injection of whole autogenous blood into the intermedullary spaces of the mandibles of seven young

dogs, it was apparent that a hemorrhagic cyst was not created in these dogs. Intermedullary hematomas were formed, as demonstrated in the two-day dog by the hemorrhagic areas in the marrow spaces. The hemorrhage was apparently resorbed by the inflammatory process, however, as demonstrated by the lack of frank hemorrhage in the ten-day, three-week, and four-week dogs.

The reaction in the ten-day, three-week, and four-week dogs was centered around the burr hole that was drilled in the cortical plate for injection of the blood. The reaction was the typical response to any irritant, namely, that of inflammation and repair. The bony fragments and necrotic edges of the burr hole were gradually resorbed by the inflammatory process. The area was organized by proliferating loose fibrous tissue which attempted to fill in the burr hole or wall off the area of debris. As the time element in this series was increased, the loose fibrous tissue was progressively replaced by denser fibrous tissue. Some of the loose fibrous tissue cells had differentiated into osteoblasts. The osteoblasts had laid down spicules of new bone at the bottom and sides of the cavity caused by the burr hole and the inflammatory process. The amount of new bone formed became progressively greater in the three- and four-week dogs.

One can safely speculate that if this experiment were run over a period of five or six months the area of the burr hole would become completely filled in with new, immature bone. The immature bone would then be replaced by mature cortical bone, completely eliminating any signs of the burr hole in six months' time.

In conclusion, one might say that the intermedullary hematoma produced by injecting whole autogenous blood into the intermedullary spaces of the mandibles of these seven dogs did not produce hemorrhagic cysts. The response was one of inflammation and repair, caused by the trauma of drilling a hole in the cortical plate for injection of the blood. Therefore, the development of a hemorrhagic cyst must depend on some other factor or factors than hemorrhage into the intermedullary spaces.

REFERENCES

1. Bernier, J. L.: The Management of Oral Disease, St. Louis, 1955, The C. V. Mosby Company, p. 465.
2. Lazansky, J. P., Wuehrmann, A. H., and Glickman, I.: Traumatic Cyst of the Mandible, Am. J. Orthodontics & Oral Surg. 31: 113-115, 1945.
3. Robinson, R. A.: Traumatic Hemorrhagic Cyst of the Mandible in an Infant, J. Am. Dent. A. 32: 774-775, 1945.
4. James, A. G., Coley, B. L., and Higginbotham, N. L.: Solitary (Unicameral) Bone Cyst, Arch. Surg. 57: 137-147, 1949.
5. Stewart, M. J., and Hamel, H. A.: Solitary Bone Cyst, South. M. J. 43: 927-936, 1950.
6. McLachlin, A. D.: Treatment and Results in Localized Osteitis Fibrosa Cystica (the Solitary Bone Cyst), J. Bone & Joint Surg. 25: 777-790, 1943.
7. Coley, B. L.: Neoplasms of Bone, New York, 1949, Paul B. Hoeber, Inc.
8. Geschickter, C. F., and Copeland, Murray M.: Tumors of Bone, ed. 3, Philadelphia, 1949, J. B. Lippincott Company, p. 250.
9. Jaffe, H. L., and Lichtenstein, L.: Solitary Unicameral Bone Cyst, Arch. Surg. 44: 1004-1025, 1942.
10. Lucas, C. D.: Cysts of the Jaw, J. Am. Dent. A. 16: 659-660, 1929 (quoted by Blum[11]).
11. Blum, T.: Unusual Bone Cavities in the Mandible: A Report of Three Cases of Traumatic Bone Cysts, J. Am. Dent. A. 19: 281-301, 1932.

12. Rushton, M. A.: Solitary Bone Cysts in the Mandible, Brit. D. J. 81: 37-49, 1946.
13. Olech, E., Sicher, H., and Weinmann, J. P.: Traumatic Mandibular Bone Cysts, ORAL SURG., ORAL MED. & ORAL PATH. 4: 1160-1172, 1951.
14. Whinery, J. G.: Progressive Bone Cavities of the Mandible, ORAL SURG., ORAL MED. & ORAL PATH. 8: 903-916, 1955.
15. Geschickter, C. F., and Copeland, Murray M.: Tumors of Bone, ed. 3, Philadelphia, 1949, J. B. Lippincott Company, p. 260.
16. Monckeberg: Über Cystenbildung bei Ostitis fibrosa, Verhandl. d. deutsch. path. Gesellsch. 7: 232, 1904.
17. Konjetzny, G. E.: Die sogenannte "lokalisierte Ostitis fibrosa," Arch. f. klin. Chir. 121: 566, 1922.
18. Thoma, K. H.: Oral Pathology, St. Louis, 1950, The C. V. Mosby Company, p. 915.
19. Jaffe, H. L.: Giant Cell Reparative Granuloma, Traumatic Bone Cyst and Fibrous (Fibro-Osseous) Dysplasia of the Jawbones, ORAL SURG., ORAL MED. & ORAL PATH. 6: 159, 1953.
20. Von Mickulicz, J.: Über cystische Degeneration der Knocken, Verhandl. d. Gesellsch. deutsch. Naturforsch. u. Aerzte 76: 107, 1906.
21. Boetticher: Über Knochenzysten im Humerus, Zentralbl. f. Chir., No. 27, p. 157, 1904.
22. Beneke, R.: Verhandl. d. deutsch. pathol. Gesellsch., Part 1, p. 240, 1904.
23. Pommer, G.: Zur Kenntniss der progressiven Haematom und Phlegmasieveraenderungen der Roehrenknochen auf Grund mikroskopischer Befunde im neuen Knochenzystenfalle, Hans von Haberer's, Arch. f. orthop. u. Unfall-Chir. 17: 17, 1920.
24. Waldron, C. A.: Solitary (Hemorrhagic) Cyst of the Mandible, ORAL SURG., ORAL MED. & ORAL PATH. 7: 88, 1954.

221 ANGELL ST.

# RESPONSE OF THE PERIODONTIUM, PULP, AND SALIVARY GLANDS TO GINGIVAL AND TOOTH INJURY IN YOUNG ADULT MALE RATS

## I. Periodontal Tissues

*S. S. Stahl, D.D.S., M.S.,* New York, N. Y.*

PERIODONTAL as well as endodontic pathology consists essentially of injury followed by inflammation and the sequelae of this process. The purpose of this study was to investigate the responses of the affected tissues to an experimentally induced injury by both histologic and histochemical methods and to compare these changes to those observed in wound healing at other sites.

### MATERIAL AND METHODS

Seventy male rats of the Long-Evans strain, weighing an average of 200 grams at the beginning of the experiment, were utilized in this study. The injury was created with a cross-cut fissure burr reshaped to the thinnest diameter possible, by drilling a channel through the interproximal space between the maxillary first and second molars. The channel was extended occlusally, removing the dental contact and thus allowing continuous food impaction to take place. This procedure removed the gingival papilla. Care was taken to keep the injury away from the alveolar crest as much as possible. The channel also cut into the adjacent tooth structures. This led to pulpal exposure in most instances.

All animals were fed ad libitum. The animals were sacrificed at various time intervals (usually daily) in groups of two. The injured maxilla and submaxillary and sublingual glands were dissected out and prepared for histologic study.

The maxilla was serially sectioned, and alternate sections were treated by the following techniques: hematoxylin and eosin, Wilder's silver impregnation† periodic acid–Schiff (PAS) stain and allochrome modification,† enzyme digestion

From the Murry and Leonie Guggenheim Foundation, Institute for Dental Research, and the Department of Periodontia and Oral Medicine, New York University College of Dentistry.

This study was supported in part by Grant-in-Aid #D-537 from the Institute for Dental Research, National Institutes of Health, United States Public Health Service, Bethesda, Maryland.

*Assistant Professor, Department of Periodontia and Oral Medicine, New York University.

†Lillie, R. D.: Histopathologic Technic and Practical Histochemistry, New York, 1954, The Blakiston Company.

with testicular hyaluronidase (three-hour digestion),* metachromatic method (toluidine blue).†

Salivary glands were cut in half. Most specimens were fixed in formalin, while a representative group was fixed in alcohol. Serial sections were obtained, and alternate sections were stained with hematoxylin and eosin, periodic acid–Schiff stain, and Mallory's connective tissue stain.†

## OBSERVATIONS

In all sections studied the experimentally created channel had cut into the dentine of the adjacent teeth, creating a defect. The most apical edge of the defect was regarded as the reference point for the most apical extent of the injury.

For the sake of clarity, the tissue response to the injury will be described by time intervals.

Fig. 1.—Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed immediately after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

*Immediately After Injury (Fig 1).*—Epithelium and underlying connective tissue, as well as a small section of the alveolar crest, had been removed. The periodontal membrane immediately below the injury showed evidence of edema, and the fibers appeared homogeneous. These fibers also showed a slight fuchsinophilia which became less intense after three-hour testicular hyaluronidase digestion. Metachromatic staining showed areas of beta metachromasia in the periodontal membrane fibers immediately below the injury. Some fibers attaching to the alveolar bone at the crest appeared argyrophilic.

*Three Hours After Injury (Fig. 2).*—The surface of the lesion was covered with necrotic debris. The connective tissue immediately below the injury appeared homogeneous and contained areas of necrosis. Some polymorphonuclear

*Pearce, A. G. E.: Histochemistry, Boston, 1953, Little, Brown & Company.

†Jones, R. McClung: McClung's Handbook of Microscopic Technique, ed. 3, New York, 1950, Paul B. Hoeber, Inc.

*A.*

*B.*

*C.*

Fig. 2.—*A*, Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed three hours after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 5/10.)

*B*, Serial section of specimen shown in *A*. (Periodic acid–Schiff allochrome stain. Magnification, ×60; reduced 5/10.)

*C*, Serial section of specimen shown in *A*. (Silver impregnation stain. Magnification, ×60; reduced 5/10.)

leukocytes and red blood cells were seen in the area. Of interest was the appearance of coronally oriented blood vessels in the periodontal membrane which led to the site of injury. These vessels were full of blood elements. Edema was noted in an increasing area of the periodontal membrane. The fibers immediately below injury stained fuchsinophilic and were more strikingly argyrophilic than the more apically situated periodontal membrane fibers. Enzyme digestion reduced the fuchsinophilia. Orthometachromasia was noted in these surface fibers.

*Six Hours After Injury (Fig. 3).*—Necrotic material was present at the surface of the injury. The underlying connective tissue fibers stained brightly with hematoxylin and eosin, and the bundles appeared confluent. Below these bundles, areas of collagen necrosis, red blood cells, and polymorphonuclear leukocytes could be seen. Small vessels from the periodontal membrane appeared to enter this area. Of interest was the presence of inflammatory cells surrounding the vessels within the alveolar crest or within the marrow spaces near the crest. Areas of resorption were also noted at the crest. The fibers beneath the injury showed a marked fuchsinophilia which was slightly reduced by enzyme digestion; these fibers were markedly argyrophilic and exhibited beta metachromasia.

*Twenty-four Hours After Injury (Fig. 4).*—Necrosis and ulceration were noted at the site of injury. Polymorphonuclear leukocytes, which dominated the cellular infiltrate, were found in large numbers at the site of injury. Polymorphonuclear leukocytes were also seen to be present throughout the transseptal fibers, between fiber bundles of the periodontal membrane, below the alveolar crest, and in the marrow spaces near the crest. Areas of the alveolar crest showed evidence of resorption. There was edema in the transseptal fibers, with areas of necrosis. The fibers below injury appeared strongly PAS-positive and argyrophilic. Metachromatic staining appeared to be reduced.

*Forty-eight Hours After Injury (Fig. 5).*—In one specimen, marked apical migration of the epithelial attachment was noted. The epithelial layer had increased in thickness and showed a markedly widened keratin layer when compared to the epithelium of the noninjured papilla of the neighboring tooth. Of special interest was the resorption of the entire interdental septum with replacement by loosely organized connective tissue in forty-eight hours. The connective tissue contained many round cells, as well as young fibroblasts and capillaries. The above-described connective tissue fibers stained fuchsinophilic. They did not demonstrate metachromatic staining, however, and they contained comparatively few argyrophilic fibers.

*Two to Four Days After Injury (Fig. 6).*—Surface necrosis and ulceration were seen in all specimens at the site of injury. Below the necrotic tissue, many inflammatory cells (both polymorphonuclear leukocytes and round cells) were present. The underlying connective tissue appeared homogeneous and showed areas of degeneration. The alveolar bone at the crest was necrotic, as evidenced by empty lacunar spaces. Inflammatory cells were also seen within the marrow

*A.*

*B.*

*C.*

Fig. 3.—*A*, Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed six hours after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

*B*, Serial section of specimen shown in *A*. (Periodic acid–Schiff stain. Magnification, ×60; reduced 3/10.)

*C*, Serial section of specimen shown in *A*. (Silver impregnation stain. Magnification, ×60; reduced 3/10.)

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed twenty-four hours after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

Fig. 5.—Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed forty-eight hours after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

Fig. 6.—Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed three days after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

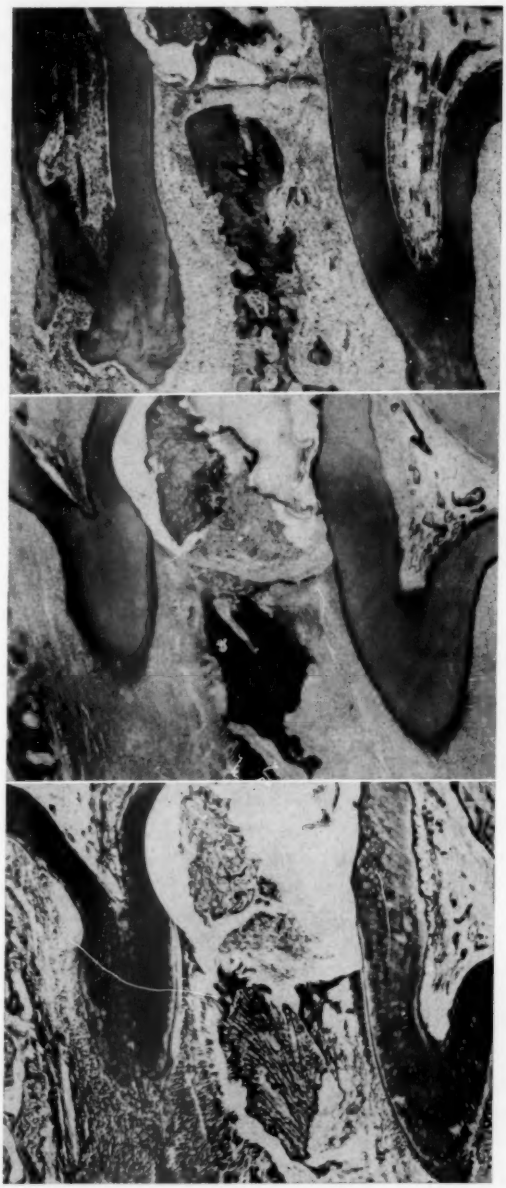


Fig. 7.—*A*, Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed five days after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

*B*, Serial section of specimen shown in *A*. (Periodic acid–Schiff stain. Magnification, ×60; reduced 3/10.)

*C*, Serial section of specimen shown in *A*. (Silver impregnation stain. Magnification, ×60; reduced 3/10.)

spaces near the alveolar crest. Osteoclastic activity was noted near these inflammatory cell accumulations. Resorption of alveolar crestal bone was present in all specimens. The periodic acid–Schiff reaction of the connective tissue elements below the injury appeared lessened, as were metachromasia and silver affinity, when compared with the reactions seen twenty-four and forty-eight hours after injury.

*Five Days After Injury (Fig. 7).*—A thin layer of epithelium was seen to bridge the wound. The underlying connective tissue stained pale and appeared diffuse. A marked reduction in granulation tissue appeared to have taken place below the epithelium, although many polymorphonuclear leukocytes were seen within the periodontal membrane below the alveolar crest. At this level, young fibroblasts and capillaries were noted. The crestal surface of the alveolar bone was necrotic, and sequestrum formation was in progress. Fuchsinophilic fibers were present near the alveolar crest but stained less intensely than those seen in twenty-four hour specimens. Many fine argyrophilic fibers were seen throughout the peridontal membrane. The fibers at the crest showed the greatest affinity for silver.

*Five to Twelve Days After Injury (Fig. 8).*—Most specimens showed marked ulceration with necrosis and sequestrum formation. Epithelization of the wound was present to various degrees of completion, and granulation tissue was noted below the area of injury. The older specimens showed a reduction in inflammatory cells, a reduction in granulation tissue, and a varying increase in collagen fibers. The increase in collagen fibers appeared to be associated with increased epithelization of the wound. Metachromasia and fuchsinophilia of the fibers below the injury seemed to be markedly lessened.

*Thirteen to Twenty-one Days After Injury (Fig. 9)*—Epithelization of the wound appeared to be completed in all specimens studied. The epithelial layer increased in size, with parakeratosis or keratosis present at the surface. Gingival and transseptal fibers showed evidence of organization, although granulation tissue and some inflammatory cells were still present. Many young fibroblasts were seen in the periodontal membrane. Apposition was usually noted at the alveolar crest. The extent of healing varied with the extent of injury in the various animals. The healing process described above, however, had taken place in all animals studied. It should also be noted that alveolar crest resorption had occurred in all cases, extending in some specimens to the apical level. Apposition of bone at the new level, however, was uniformly present. In specimens in which alveolar crest resorption involved the entire alveolar septum, connective tissue fibers extended from the cementum to the cementum of the neighboring tooth. The connective tissue fibers below the injury were less fuchsinophilic than those seen in the early specimens. Hyaluronidase digestion lessened the fuchsinophilia. Metachromasia was not noted, and reticulin fibers appeared to be gradually replaced by collagen fibers.

*Twenty-two to Thirty Days After Injury (Fig. 10).*—Apical migration of the epithelial attachment was noted in all specimens studied. The epithelial layer was keratinized and showed rete peg formation. It should be noted that

Fig. 8.

Fig. 9.

Fig. 10.

Fig. 8.—Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed ten days after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

Fig. 9.—Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed fourteen days after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

Fig. 10.—Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed twenty-seven days after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

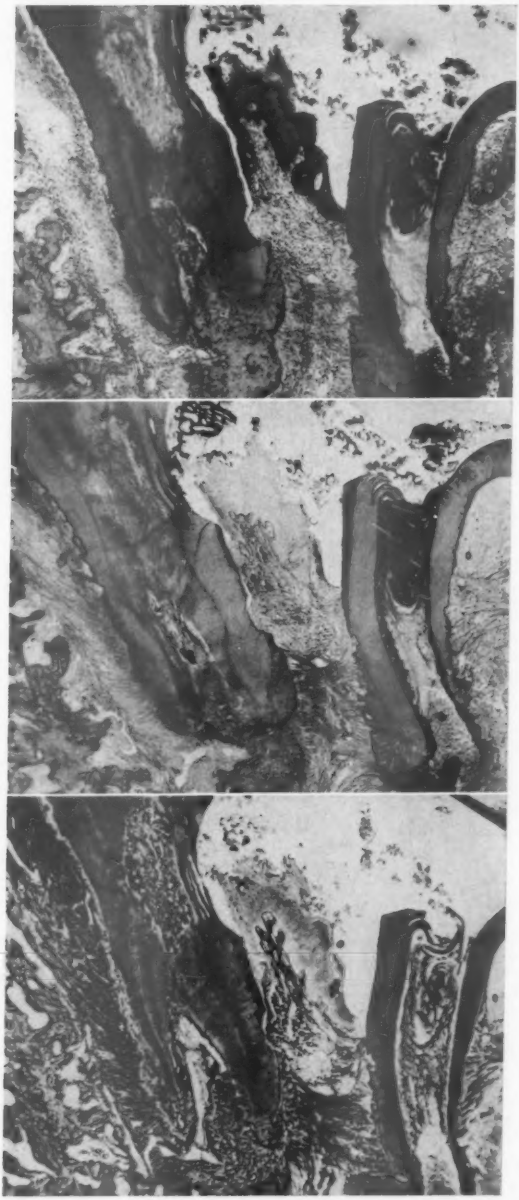


Fig. 11.—*A*, Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed thirty-three days after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

*B*, Serial section of specimen shown in *A*. (Periodic acid–Schiff stain. Magnification, ×60; reduced 3/10.)

*C*, Serial section of specimen shown in *A*. (Silver impregnation stain. Magnification, ×60; reduced 3/10.)

the epithelium of the gingival papilla between the second and third molars, which had not been injured, never showed this degree of keratinization. The increase in keratin may represent a protective adaptation of the epithelium at the site of injury to the continuous irritation from food impaction. The underlying connective tissue demonstrated further evidence of organization with reduction of inflammatory cells and granulation tissue. In some animals marked alveolar crest resorption was accompanied by a cellular increase in the periodontal membrane attached to the alveolar bone, which suggests a compensatory mechanism for the loss of bone height and attachement apparatus. It thus may represent an attempt to maintain the function of the tooth despite the marked resorption of alveolar crest. Sections prepared with periodic acid–Schiff stain showed a thicker basement membrane than was seen in the earlier specimens, and fuchsinophilic fibers were evident below the epithelium. An ortho to beta metachromasia was observed in this area. Reticulin fibers were increasingly evident in the connective tissue below the epithelium.

Fig. 12.—Photomicrograph of a mesiodistal section of the first and second maxillary molars of a rat sacrificed forty-one days after injury. (Hematoxylin and eosin stain. Magnification, ×60; reduced 3/10.)

*Thirty-one to Forty-four Days After Injury (Fig. 11).*—The epithelial layer appeared heavily keratinized and thickened. The epithelial attachment had migrated apically to about the middle third of the root. The underlying connective tissue appeared better organized, although some inflammatory cells were noted throughout the fiber bundles. The presence of inflammatory elements at this late date was probably the result of irritation due to food impaction. Alveolar bone in many specimens had resorbed to the apical level and was replaced by fibrous connective tissue. Apposition, however, was noted at the present crest level. The basement membrane stained PAS positive and appeared widened and distinct. The connective tissue fibers replacing the interdental alveolar bone showed moderate fuchsinophilia, which became less intense after

hyaluronidase digestion; these fibers also showed an ortho to beta metachromasia. Argyrophilic fibers were seen in this area among increasing numbers of collagen fibers.

A forty-one-day specimen, in which the injury was contained primarily within the coronal portion of the tooth, showed some apical migration of the epithelial attachment, with marked organization of the underlying connective tissue. Of specific interest was the extent of crestal apposition, which indicated the degree of healing response possible under favorable conditions (Fig. 12).

## DISCUSSION

*Creation of the Injury.*—The technique for gingival injury outlined in this study appears to be well suited for the investigation of gingival healing in the presence of various environmental factors. The simplicity of the operation lends itself to the handling of many animals in a relatively short time. The channel cut into the dentine of the proximal teeth provides a permanent reference point of the most apical extent of the injury, thus serving as a guide for the study of subsequent epithelial attachment position.

*Healing of the Gingival Wound.*—The sequence of soft tissue response observed in this study is similar to those observed in human gingival specimens following various techniques of gingival surgery,[1-3] as well as in dogs and guinea pigs following gingivectomy.[4, 5] In human experience, epithelization occurred four to nine days following surgery, and an essentially normal-appearing gingiva was observed after thirty days. Similar responses in wound healing have also been noted at other sites.[6-8] Of special interest, however, was the specific gingival tissue adaptation to individual requirements, such as the increased keratinization and thickening of the epithelial layer in response to chronic irritation and the increased cellularity of the periodontal membrane attached to the remaining bone in areas of marked crestal resorption.

The apparent interrelation of growth of granulation tissue and epithelization noted in this study concurs with Howes'[9] observation that epithelization does not take place over exuberant granulations. The recognition of this interrelation may be of particular significance to periodontists, who often wish to delay epithelization in order to allow for connective tissue reattachment.

Of special interest also was the forty-eight-hour specimen which demonstrated complete resorption of the interdental alveolar crest and replacement by fibrous connective tissue within this time period. The speed at which this process occurred suggests a similarity to the extremely rapid resorption of alveolar bone, seen roentgenographically, in association with acute periodontal abscesses and their sequelae.

The histochemical observations suggest an initial period of shock (zero to twenty-four hours) followed by an increase in ground substance that reaches its peak after three to six days. With an increase in fiber formation, labile ground substance appears to be reduced, as evidenced by the reduction in fuchsinophilia observed in the older specimens at the site of injury. It has been suggested that the rapid production of ground substance observed in the initial

stages of wound healing may be an early function of fibroblasts or mast cells and that it may represent the formation of collagen fibers. Dumphy and Udupa[10] thus divide wound healing into (1) a productive phase (one to five days after injury) during which mucopolysaccharides and soluble proteins, precursors of collagen, are produced, followed by (2) a collagen phase in which normal collagen fibers are formed. The present observations seem to coincide with these conclusions. The continued fuchsinophilia and argyrophilia observed in the fibers replacing a resorbed interdental septum may indicate a persistent lability of this tissue due to the functional demands placed on tooth-attaching fibers having lost their bone anchorage. These fibers may also represent a type of gingival cicatrix, since fuchsinophilia remains during cicatrization.[10]

Attempts as identification of the visualized fuchsinophilic material show it to be slightly beta metachromatic and partially hyaluronidase labile. Similar reactions have also been observed in specimens of human periodontal pathology and were interpreted as being indicative of the presence of mucoproteins and hyaluronic acid.[11]

## SUMMARY AND CONCLUSIONS

A technique for the creation of a reproducible gingival injury in young male rats has been described.

It was noted that, following injury, the gingival tissues respond as follows:

1. There was an initial shock phase (zero to three hours after injury) during which little change was noted.

2. Then came an inflammatory phase (three hours to five days after injury) during which necrosis, the inflammatory cellular infiltrate, and granulation tissue formation became evident. These processes were associated with marked enzymatic activity, as evidenced by the increased fuchsinophilia noted in the area.

3. Finally, there was a regenerative phase (five to thirty days after injury) during which epithelization of the wound, organization of the underlying connective tissue, and increase in collagen formation gradually took place. These changes were associated with a decrease in fuchsinophilic and argyrophilic fibers in the area. Complete reduction of inflammation did not occur in this study because of the continuous irritation of food impaction.

The changes described following this experimental procedure are similar to those observed following gingivectomy and surface wound healing in other sites.

## REFERENCES

1. Bernier, J. L., and Kaplan, H.: Repair of Gingival Tissue After Surgical Intervention, J. Am. Dent. A. 35: 697, 1947.
2. Lundquist, G. R.: The Zero Crevice in the Management of Periodontal Involvements, J. Am. Dent. A. 27: 837, 1940.

3. Orban, B., and Archer, E. A.: Dynamics of Wound Healing Following Elimination of Gingival Pockets, Am. J. Orthodontics & Oral Surg. **31**: 40, 1945.
4. Waerhaug, J., and Loe, H.: Tissue Reaction to Gingivectomy Pack, ORAL SURG., ORAL MED. & ORAL PATH. **10**: 923, 1957.
5. Turesky, S. S., and Glickman, I.: Histochemical Evaluation of Gingival Healing in Experimental Animals on Adequate and Vitamin C Deficient Diets, J. D. Res. **33**: 273, 1954.
6. Williamson, M. B.: The Healing of Wounds, New York, 1957, McGraw-Hill Book Company, Inc.
7. Allgower, M.: The Cellular Basis of Wound Repair, Springfield, Ill., 1956, Charles C Thomas.
8. Huebsch, R. F., Coleman, R. D., Frandsen, A. M., and Becks, H.: The Healing Process Following Molar Extraction. I. Normal Male Rats, ORAL SURG., ORAL MED. & ORAL PATH. **5**: 864, 1952.
9. Howes, E. L.: Wound Healing, J. Periodont. **28**: 376, 1957.
10. Dumphy, J. E., and Udupa, K. N.: Chemical and Histochemical Sequences in the Normal Healing of Wounds, New England J. Med. **253**: 847, 1955.
11. Stahl, S. S., Sandler, H. C., and Subin, E.: Histochemical Reactions in Periodontal Disease, J. Periodont. **29**: 183, 1958.

## Section by the

## ARMED FORCES AND PUBLIC HEALTH SERVICE

. . . . . .

# DOUBLE LIP

## Report of a Case

*George Swerdloff, Lieutenant Colonel, DC, USA**

ALTHOUGH double lip may involve either lip, it affects the upper lip more frequently than the lower.[1] It consists of an accessory fold of redundant tissue in the mucosal portion of the lip just inside the vermilion border. Its appearance is especially noticeable in the upper lip when the lip is drawn taut across the upper teeth, as in the act of smiling. It is believed that this is a developmental anomaly[2] which is present at birth but is not noticed until after the teeth have erupted. Constantly sucking the redundant tissue or drawing it between the teeth may cause it to increase in size.[3] Because of its conspicuousness, this deformity may lead to personality problems. Surgical intervention can effect a cosmetic correction.

CASE REPORT

A 30-year-old Caucasian man, a noncommissioned officer, was referred for removal of an upper labial frenum incidental to periodontal treatment. Examination disclosed a double lip, and the patient was informed of this finding. He stated that it had been there as long as he could remember and that it did not bother him. The frenectomy was performed, and the patient was dismissed. Two weeks later he returned and said that since the frenectomy his accessory lip had interfered with speaking and he had become quite conscious of it. He asked that it be removed. Fig. 1 shows the patient smiling immediately prior to surgery.

*Operation.*—An intraoral injection of 2 per cent Xylocaine was made bilaterally into the infraorbital region. The redundant tissue was visualized and outlined with gentian violet. The tissue was grasped with small mosquito hemostats along the entire extent of the outlined area. At this time another 2 c.c. of Xylocaine was infiltrated into the operative field for the purpose of controlling hemorrhage. With scalpel and scissors, mucous membrane and submucous tissue were excised along the entire extent of the clamped deformity.

From the Dental Service, Fort McPherson, Georgia.
*Now assigned to 207th Medical Detachment (DS), APO 7, c/o Postmaster, San Francisco, California.

The adjacent margin of mucous membrane was undermined, and the wound margins were approximated with interrupted 6-0 black silk sutures. A piece of adhesive tape was placed tightly over the outside of the upper lip to act as a pressure dressing.

The excised tissue was submitted to a pathologist, who returned the following report:

*Microscopic:* The tissue is covered with stratified squamous epithelium. Hyperkeratosis and parakeratosis are present. There is marked acanthosis. The underlying stroma is composed of dense fibrous tissue, which is well vascularized. There is salivary gland tissue at the base of the lesion.

*Diagnosis:* Pachyderma oris clinically involving an accessory lip.

Fig. 1.

Fig. 2.

*Postoperative Course.*—There was minimal swelling which disappeared by the fifth postoperative day, at which time the sutures were removed. Paresthesia of a small area of the upper lip persisted for two months. Fig. 2 shows the patient's lip three weeks after the operation.

## COMMENT

The removal of a double lip is a relatively simple operation which can be performed as an office procedure under local anesthesia. Cosmetic correction can be achieved with a minimum of postoperative discomfort.

REFERENCES

1. Dingman, R. O.: Double Lip, J. Oral Surg. 5: 146, 1947.
2. Cheraskin, E., and Langley, L. L.: Dynamics of Oral Diagnosis, Chicago, 1956, The Year Book Publishers, Inc.
3. Thoma, K. H.: Oral Surgery, ed. 2, St. Louis, 1952, The C. V. Mosby Company, vol. II.

# DEVELOPMENT AND CLINICAL INVESTIGATION OF A NEW ORAL SURFACE ANESTHETIC FOR ACUTE AND CHRONIC ORAL LESIONS

*Irwin I. Ship, D.M.D.,* Anderson F. Williams, D.M.D.,** and Boris J. Osheroff, B.S.,*** Bethesda, Md.*

## INTRODUCTION

THE search for an ideal surface anesthetic agent for topical application in the oral cavities of patients with severe, acute and chronic, ulcerative, desquamative, and traumatic conditions of the oral mucous membranes has been continuous. Relief of pain is of paramount importance, as eating, speaking, and over-all comfort are severely compromised in these patients. Although locally applied anesthetics have demonstrated broad applications in dentistry, as well as in medicine, the present report is limited to the use of anesthetic agents in patients with severe pain as a result of acute and chronic oral lesions.

Topical anesthesia has not been entirely free from ill effects. Campbell and Adriani[1, 2] reported that reactions from locally applied anesthetics were most commonly seen following topical application to the mucous membranes. Most of the reactions were associated with high plasma drug levels due to rapid absorption and/or the use of large quantities of drug. Absorption of cocaine and tetracaine from the mucous membranes of the pharynx resulted in drug levels comparable to those seen following intravenous injections. These findings were limited to normal mucosal tissues and single drug applications. In patients with ulcerated and otherwise damaged mucous membranes, who receive multiple daily applications of anesthetic agents over extended periods of time, it is reasonable to suspect that toxic reactions occur more frequently than has been recognized.

The ideal topical anesthetic for chronic oral conditions should have the following characteristics: (1) Low toxicity, even with relatively large doses over long periods of time, both systemically and locally; (2) low sensitization potential, even after multiple topical applications; (3) rapid onset of action,

From the National Institutes of Health, United States Public Health Service, Department of Health, Education, and Welfare.
*National Institute of Dental Research.
**Dental Department, Clinical Center.
***Pharmacy Department, Clinical Center.

favorable depth of anesthesia, and long duration of anesthesia; and (4) favorable accessory properties (taste, smell, etc.). Preparations currently available for topical anesthesia have not satisfied the first of these criteria.

Since the introduction of antihistamines in 1937, there have been numerous reports of their anesthetic properties associated with low toxicity and sensitization potential.[3-8] Rosenthal and Minard[9] were the first to investigate the anesthetic properties of antihistamines. In 1947 Feinberg and Bernstein[10] showed that tripelennamine hydrochloride had considerable antipruritic and analgesic activity when applied topically to the anal mucosa. Mosely,[11] in 1948, noted marked pain relief following topical application of a 1 per cent tripelennamine hydrochloride solution to the mouth. In 1947 Leavitt and Code[12] reported that diphenhydramine hydrochloride solution, 1:500, had an anesthetic potency equivalent to procaine hydrochloride in a dilution of 1:200. In other reports, topically applied antihistamines were found to provide adequate, safe anesthesia in the skin, for gastroscopy, for urethral manipulations, and for pain relief in patients with stomatitis.[13-16]

Dyclonine hydrochloride has been the subject of clinical investigations and studies in animals which have indicated its safety and effectiveness as a topical anesthetic agent.[17-21] It has been used routinely for topical anesthesia in urologic and ophthalmologic procedures, in peroral endoscopy, in dermatology, and in dentistry.[22-28] In addition, this drug was found to be bactericidal and fungicidal.[29] Intravenous doses ranging between 200 and 500 mg., given to adults over a five-minute period, produced side effects only at the higher dosage levels.[30] These side effects included nausea, vomiting, vertigo, and confusion, but all were transient and no measurable cardiovascular damage occurred. Oral doses up to 1.2 grams per day were tolerated by adults for periods of from one to three weeks without side effects. McCarthy and Shklar[31] reported that 0.5 per cent dyclonine hydrochloride was highly effective for the relief of pain in patients with benign mucous membrane pemphigoid.[31]

In view of the low toxicity and high topical anesthetic potency of these drugs, further investigations of their use were indicated.

## PRELIMINARY INVESTIGATION OF COMPOUNDS AND METHODS

Various concentrations of four antihistamine compounds and dyclonine hydrochloride were prepared in isotonic saline for initial screening purposes. A 2 per cent lidocaine solution in methylcellulose, which was heretofore used routinely, was used as the reference anesthetic (Table I). Patients with acute, chronic, and recurrent ulcerative diseases of the oral mucous membranes were studied. These patients had severe pain and discomfort when eating, speaking, and performing normal oral functions. Coded solutions were given to patients for application either directly to lesions with cotton-tipped applicator sticks or in 5 ml. doses as a mouthwash. Patients were instructed to use the solution prior to meals, before bedtime, and when necessary for the relief of pain. All solutions were used for a one-week period.

Records were maintained of the quantities used, and patients were carefully questioned regarding time of onset of effective anesthesia, degree of pain relief, duration of anesthesia, and unusual reactions. Oral examinations were performed before and after the use of each solution.

TABLE I. AGENTS TESTED FOR ONE-WEEK PERIODS IN TOPICAL ANESTHESIA SCREENING PROGRAM

| AGENT | CONCENTRATIONS (PER CENT) | NO. OF PATIENTS | MEAN ONSET TIME (MINUTES) | DEPTH OF ANESTHESIA | MEAN DURATION OF ANESTHESIA (MINUTES) |
|---|---|---|---|---|---|
| Lidocaine hydrochloride | 5 | 15 | 3- 8 | Adequate | 30 |
| Dyclonine hydrochloride | 0.5 | 14 | 4- 8 | Adequate | 45 |
| | 1.0 | 12 | | | |
| | 5.0 | 13 | | | |
| Diphenhydramine hydrochloride | 0.5 | 15 | 8-12 | Inadequate | 65 |
| | 1.0 | 12 | | | |
| | 5.0 | 13 | | | |
| Tripelennamine hydrochloride | 0.5 | 13 | None | None | None |
| | 1.0 | 15 | | | |
| | 5.0 | 12 | | | |
| Promethazine hydrochloride | 0.5 | 12 | None | None | None |
| | 1.0 | 10 | | | |
| | 5.0 | 8 | | | |
| Chlorpheniramine maleate | 0.5 | 11 | None | None | None |
| | 1.0 | 11 | | | |
| | 5.0 | 9 | | | |

## RESULTS OF PRELIMINARY INVESTIGATIONS

Fifteen patients with severe recurrent aphthous stomatitis were studied over a period of six months. Due to the random nature of the treatment sequence, not every patient received each solution. Analysis of results indicated excellent depth of anesthesia with lidocaine hydrochloride and dyclonine hydrochloride and inadequate anesthesia with diphenhydramine hydrochloride (Table I). There were no perceptible differences in the depth of anesthesia produced by the various concentrations. Onset of anesthesia was rapid with lidocaine hydrochloride and dyclonine hydrochloride and somewhat delayed with diphenhydramine hydrochloride solutions. Chlorpheniramine maleate and promethazine hydrochloride demonstrated no topical anesthesia in any concentrations studied. Tripelennamine hydrochloride had very slight anesthetic effects but was poorly accepted because of its bitter taste. Duration of anesthetic effects was longest with diphenhydramine hydrochloride (mean duration, sixty-five minutes), followed by dyclonine hydrochloride (mean, forty-five minutes), and lidocaine hydrochloride (mean, thirty minutes). Once again, no differences were noted among the various concentrations studied. No adverse reactions were reported or noted after use of the above solutions, nor were there any effects other than topical anesthesia.

The results suggested that a combination of the pharmacologic effects of dyclonine hydrochloride and diphenhydramine hydrochloride would be desirable. Prolongation of the surface anesthesia resulting from dyclonine hydrochloride might be achieved by the addition of diphenhydramine hydrochloride.

### CLINICAL EVALUATION

An isotonic solution containing 0.5 per cent diphenhydramine hydrochloride and 0.5 per cent dyclonine hydrochloride was studied for anesthetic potency and duration in patients with various painful oral conditions. Onset and duration, as well as depth of anesthesia and side reactions, were investigated. As in the preliminary investigations, solutions were self-administered. Patients were questioned and examined periodically throughout the course of this study. The depth of anesthesia was graded subjectively as follows:

1. Excessive—anesthesia so profound as to cause total loss of taste and to produce uncomfortable sensations of swelling of intraoral tissues to the extent that medication was refused.
2. Excellent—anesthesia relieved pain and permitted oral functions without discomfort.
3. Adequate—anesthesia relieved pain and permitted oral functions with reduced discomfort.
4. Poor —minimal pain relief associated with little or no improvement of oral functions.

The data collected were limited to subjective responses, such as pain relief and oral comfort.

### RESULTS OF CLINICAL EVALUATION

A total of forty-five patients with painful oral lesions were observed over periods of from seven to 540 days (Table II). Onset of effective anesthesia

TABLE II. EFFECTS OF DYCLONINE HYDROCHLORIDE—DIPHENHYDRAMINE HYDROCHLORIDE ANESTHETIC SOLUTION IN ACUTE AND CHRONIC ORAL CONDITIONS

| DIAGNOSIS | NO. OF PATIENTS | MEAN AGE | MEAN DURATION OF STUDY (DAYS) | MEAN ONSET TIME (MINUTES) | MEAN DURATION OF ANESTHESIA (MINUTES) | DEPTH OF ANESTHESIA* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1 | 2 | 3 | 4 |
| Recurrent aphthous stomatitis | 24 | 29 | 240 | 5 | 80 | 1 | 8 | 13 | 2 |
| Acute herpetic gingivostomatitis | 2 | 22 | 21 | 4 | 65 | 0 | 0 | 2 | 0 |
| Lichen planus | 3 | 46 | 335 | 5 | 80 | 0 | 0 | 3 | 0 |
| Benign mucous membrane pemphigoid | 3 | 57 | 270 | 4 | 70 | 0 | 0 | 2 | 1 |
| Pemphigus vulgaris | 1 | 46 | 67 | 6 | 105 | 0 | 1 | 0 | 0 |
| Psychogenic trauma | 1 | 12 | 28 | 3 | 55 | 1 | – | – | – |
| Aplastic anemia | 2 | 55 | 63 | 4 | 75 | 0 | 1 | 1 | 0 |
| Leukemia and drug reactions | 9 | 37 | 22 | 3 | 40 | 0 | 4 | 4 | 1 |
| Totals | 45 | | | | | 2 | 14 | 25 | 4 |

*1 = Excessive anesthesia.
2 = Excellent anesthesia.
3 = Adequate anesthesia.
4 = Poor anesthesia.

occurred within three to seven minutes following application of the anesthetic solutions to the lesions or following use as a mouthwash. Depth of anesthesia ranged from excellent to poor; occasionally, it was found to be excessive. Duration of effective pain relief was approximately one hour, and often it extended to two hours. One untoward reaction was observed throughout this study: following topical application of a solution of 0.5 per cent dyclonine hydrochloride and 0.5 per cent diphenhydramine hydrochloride, a 35-year-old woman with recurrent aphthous stomatitis developed acute swelling of both lips associated with multiple severe ulcerations, malaise, fever, and headache. The general symptoms disappeared spontaneously within twenty-four hours after withdrawal of the medication, and the local drug eruption cleared rapidly in three days. The patient later reported having experienced an allergic reaction following ingestion of antihistamines in "cold tablets." Five patients reported sensations of dryness of the mouth, and three patients reported excessive salivation. The explanation of these reactions is obscure at this time.

## DISCUSSION

Local anesthetic agents have demonstrated their effectiveness in almost every medical specialty. In dentistry, topical anesthesia has been used prior to injection of anesthetic agents and for suppression of the gag reflex in oral manipulations. Used infrequently, in small doses, lidocaine hydrochloride and other topical anesthetic agents have demonstrated adequate clinical effectiveness and safety. In patients requiring topical anesthesia for the relief of pain from oral diseases, increased drug levels over extended periods of time might result in severe toxic reactions. In patients with severe, painful oral ulcerations due to leukemia or following cancer chemotherapy, large doses of these anesthetic agents might cause toxic reactions, interfering with the patient's vital therapeutic regime. It is noted in Table II that duration time of anesthesia in these patients is shorter than in the other groups studied. Likewise, the onset time of effective anesthesia is shorter. This may be due to the severe pain, constant discomfort, and general morbidity of these patients.

A topical anesthetic agent with low toxicity and sensitization potential, as well as favorable potency, has been well received by patients who have had severe pain and discomfort while eating, speaking, and performing other necessary oral activities. Self-administered, fifteen minutes prior to mealtime, before bedtime, and during other painful periods in the day, this topical anesthetic solution has been accepted by the patients as a helpful remedy.

## SUMMARY

Various solutions of antihistamines and dyclonine hydrochloride were compared with lidocaine hydrochloride as topical applications for relief of pain in patients with severe oral lesions. Preliminary screening indicated that dyclonine hydrochloride and lidocaine hydrochloride demonstrated excellent anesthetic qualities and that solutions of diphenhydramine hydrochloride produced mild

anesthesia of prolonged duration. The combination of dyclonine hydrochloride and diphenhydramine hydrochloride in saline solution produced effective anesthesia in the lowest concentrations under study. Anesthesia persisted for periods of one to two hours in forty-four patients studied for periods ranging from seven to 540 days. One allergic reaction to 0.5 per cent dyclonine hydrochloride—0.5 per cent diphenhydramine hydrochloride solution was described. Self-administered, either applied with cotton-tipped applicators directly to the mucosal lesion or used as a mouthwash, a 0.5 per cent dyclonine hydrochloride—0.5 per cent diphenhydramine hydrochloride solution gave adequate to excellent relief from pain in most of the patients studied.

We wish to express our gratitude to the following companies for their cooperation in supplying us with pure drugs for this study: Pitman-Moore Company, Indianapolis, Indiana, makers of Dyclone (dyclonine hydrochloride); Ciba Pharmaceutical Products, Inc., Summit, New Jersey, manufacturers of Pyribenzamine (tripelennamine hydrochloride); and Wyeth Laboratories, Philadelphia, Pennsylvania, makers of Phenergan (promethazine hydrochloride).

REFERENCES

1. Campbell, D., and Adriani, J.: Absorption of Local Anesthetics, J. A. M. A. **168**: 873-877, 1958.
2. Adriani, J., and Campbell, D.: Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes, J. A. M. A. **162**: 1527-1530, 1956.
3. Landau, S. W., Nelson, W. A., and Gay, L. N.: Antihistamine Properties of Local Anesthetics and Anesthetic Properties of Antihistamine Compounds, J. Allergy **22**: 19-30, 1951.
4. Stephan, C. R., Nowill, W. K., Hall, H., Martin, R., and Margolis, G.: Role of Antihistaminic Drugs in Regional and Spinal Anesthesia, Anesthesiology **15**: 601-621, 1954.
5. Betcher, A. M., and Tang, Z. T.: Pyribenzamine: Evaluation of Effectiveness as an Analgesic Agent in Regional Anesthesia, Anesthesiology **16**: 214-223, 1955.
6. Steffen, C. G., Zimmerman, M., and Mihan, R.: Diphenhydramine as a Local Anesthetic Agent, A. M. A. Arch. Dermat. **74**: 76-79, 1956.
7. Goswani, R., Das, P. C., and Phukan, D.: Local Anesthetic Action of Antihistaminics (Promethazine Hydrochloride and Mepyramine Maleate), Indian J. M. Sc. **12**: 63-71, 1958.
8. Simon, S. W., Beard, A. B., and Willoughby, D. W.: A Safe Effective Local Anesthetic in Dentistry, Mil. Med. **123**: 377-380, 1958.
9. Rosenthal, S. R., and Minard, D.: Experiments on Histamine as the Chemical Mediator for Cutaneous Pain, J. Exper. Med. **70**: 415-425, 1939.
10. Feinberg, S. M., and Bernstein, T. B.: Tripelennamine (Pyribenzamine) Ointment for the Relief of Itching, J. A. M. A. **134**: 874-875, 1947.
11. Mosely, V.: Use of Tripelennamine Hydrochloride (Pyribenzamine) as a Topical Anesthetic, Am. J. Digest. Dis. **15**: 410-411, 1948.
12. Leavitt, M. D., and Code, C. F.: Anesthetic Action of Beta-Dimethyl-Aminoethyl Benzydryl Ether Hydrochloride (Benadryl) in the Skin of Human Beings, Proc. Soc. Exper. Biol. & Med. **65**: 33-38, 1947.
13. Steffen, C. G., Mihan, R., and Zimmerman, M.: The Evaluation of Various Antihistamines as Local Anesthetic Agents, J. Invest. Dermat. **29**: 7-8, 1957.
14. Reynolds, J., Kahn, A. G., Jr., and Levy, J. S.: Use of Antihistamine Drugs for Local Anesthesia of Gastroscopy, Gastroenterology **14**: 535-537, 1950.
15. Fitzpatrick, R. J., Orr, L. M., and Stubbart, F. J.: Antihistamines as Local Anesthetic Agents for Urethral Manipulation, J. A. M. A. **150**: 1092-1094, 1952.
16. Stubbart, F. J.: The Use of Antihistamines as Local Anesthetic Agents, J. Florida M. A. **39**: 505-506, 1953.
17. Richards, A., Abreu, B. E., Bockstahler, E. R., and Wright, D. L.: General Pharmacology of 4-alkoxy-B-(1-piperidyl) Propriophenones, Fed. Proc. **11**: 385, 1952.
18. Hungerford, L.: Dyclonine: A New Topical Anesthetic, Bull. Mason Clinic **9**: 105-108, 1955.

19. Abreu, B. E., Richards, A. B., Weaver, L. C., Burch, G. R., Bunde, C. A., Bockstahler, E. R., and Wright, D. L.: Pharmacologic Properties of 4-alkoxy-B-(1-piperidyl) Propriophenones, J. Pharmacol. & Exper. Therap. **115**: 419-426, 1955.
20. Arora, R. B., and Sharma, V. N.: Local Anesthetic and Pharmacological Properties of 4n-butoxy B-(1-piperidyl) Propriophenone Hydrochloride and B-diethylaminoethyl p-n-hexylobenzilate Hydrochloride, J. Pharmacol. & Exper. Therap. **115**: 413-418, 1955.
21. Morginson, W. J., Rich, C. O., Eskelson, Y. D., Kirkman, L. W., Utterback, M., Burton, A. M., and Coletti, J. M.: Dyclonine Hyrdochloride: A New Topical Antipruritic Agent, Postgrad. Med. **19**: 605-607, 1956.
22. Fisher, H. E.: Dyclonine Hydrochloride; Evaluation of a New Topical Anesthetic in Minor Urologic Techniques, Missouri Med. **52**: 943-944, 1955.
23. Arora, B., Consul, B. N., Sharma, V. N., and Kulshrestha, P. P.: Clinical Trial of Dyclonine in Intraocular Ophthalmic Surgery, Eye, Ear, Nose & Throat Monthly **34**: 593-605, 1955.
24. Hughs, F.: Use of a New Topical Anesthetic Agent (Dyclone) in Peroral Endoscopy, J. Thoracic Surg. **32**: 135-136, 1956.
25. Harris, L., Parry, J. C., and Greifenstein, F. E.: Dyclonine—a New Local Anesthetic Agent: Clinical Evaluation, Anesthesiology **17**: 648-652, 1956.
26. Shelmire, B., Gastineau, F. M., and Shields, T.: Evaluation of a New Topical Anesthetic, Dyclonine Hydrochloride, A. M. A. Arch. Dermat. **71**: 728-730, 1955.
27. Ping, R. S., White, J. G., and Spear, L. B.: Dyclonine Hydrochloride as a Topical Anesthetic in Dentistry; a Preliminary Report, ORAL SURG., ORAL MED. & ORAL PATH. **10**: 623-626, 1957.
28. Thomason, J. H.: Dyclonine in General Dental Practice, J. South. California D. A. **26**: 242-243, 1958.
29. Florestano, H. J., and Bahler, M. E.: Antimicrobial Properties of Dyclonine Hydrochloride, a New Topical Anesthetic, J. Am. Pharm. A. (Scient. Ed.) **45**: 320-325, 1956.
30. Abreu, B. E., Richards, A., and Burch, G. R.: Nervous System Effects of 4-alkoxy-p-(1-piperidyl) Propriophenone, Fed. Proc. **11**: 317, 1952.
31. McCarthy, P. L., and Shklar, G.: Benign Mucous Membrane Pemphigus, New England J. Med. **258**: 726-731, 1958.

# ANNOUNCEMENTS

## New York Institute of Clinical Oral Pathology, Inc.

A course in clinical oral pathology will be given on two Wednesday evenings a month, October through May, from 7:30 to 10 P.M. (sixteen sessions). The class will be limited to thirty students.

The course will include lectures on embryology, hematology, histology and pathology (illustrated by lantern slides, blackboard demonstration, microscopic slides, etc.) and their clinical interpretation. Case reports stressing history, clinical findings, x-ray studies, diagnosis, treatment (including diagnostic and surgical procedures), histopathologic evidence, and prognosis will be given by the staff of the Institute and guest speakers. The course is approved by the Board of Education of the University of the State of New York.

Inquiries should be addressed to the Executive Secretary, 101 East 79th St., New York 21, New York.

---

## Oral Pathology Laboratory of Mount Sinai Hospital

The final clinical oral pathology conference of the season will be held at 5 P.M. on Friday, May 13, 1960. The topic will be "The Early Detection of Oral Cancer—The Responsibility of the Dentist," and the speaker will be Dr. Lester R. Cahn.

The conference will be held in Lecture Room 3-B on the third floor of the Administration Building, Mount Sinai Hospital, New York, New York.

---

## Boston University and Massachusetts Memorial Hospitals

The Department of Stomatology, Division of Graduate Studies, School of Medicine, Boston University and the Massachusetts Memorial Hospitals, announces the following postgraduate courses:

FULL MOUTH RECONSTRUCTION. May 16 to 20, 1960. Leo Talkov, David J. Baraban, Henry M. Goldman, Bernard S. Chaikin, and Gerald M. Kramer. Enrollment limited to fifteen students. Fee, $200.00.

This course is intended to correlate all the phases of oral diagnosis and therapeutics that are involved in the restoration of the masticatory apparatus to a healthy, functional state. Detailed explanations of the prosthetic procedures will be given. Clinical demonstrations will include the technics of periodontal therapy, occlusal analysis, and restorative procedures.

SURGICAL TECHNICS EMPLOYED IN PERIODONTAL THERAPY. May 23 to 27, 1960. Lewis Fox, D.D.S., F.A.C.D., Associate Professor of Periodontology, Graduate School of Medicine, University of Pennsylvania, and Associate Clinical Professor of Dentistry, Faculty of Medicine, School of Dental and Oral Surgery, Columbia University. Enrollment limited to twelve students. Fee, $200.00.

This course is designed to familiarize the student with the various surgical technics employed in periodontal therapy. Demonstrations on patients will also be given.

Applications must be accompanied by a check for the full amount for each course, payable to Massachusetts Memorial Hospitals, and should be sent to Director, Postgraduate Courses, Department of Stomatology, Massachusetts Memorial Hospitals, 750 Harrison Ave., Boston 18, Massachusetts.

---

## University of North Carolina

The School of Dentistry announces the following postgraduate courses:

Clinical Periodontia and Oral Pathology. June 7 to 11, 1960. Tuition, $200.00.

Dentistry for Children. July 11 to 15, July 18 to 22, and July 25 to 29, 1960. Tuition, $100.00 for each course.

Further information may be obtained from the Office of Postgraduate Dental Instruction, School of Dentistry, P. O. Box 750, Chapel Hill, North Carolina.

---

## University of Pennsylvania

Drs. Henry M. Goldman and D. Walter Cohen will present an advanced course in periodontal therapy at the School of Dentistry, University of Pennsylvania, May 16 to 20, 1960. The instruction will be directed toward treatment planning with emphasis on periodontal therapy. There will be clinical and television demonstrations of the technical procedures.

For further information, please write to Postgraduate Courses, School of Dentistry, University of Pennsylvania, 4001 Spruce St., Philadelphia 4, Pennsylvania.

---

## Georgetown University

A postgraduate course in intravenous anesthesia for the dental office will be given from 9 A.M. to 5 P.M., May 22 to 26, 1960, by Drs. Harold Krogh of Washington, D. C., and Edward Driscoll of Bethesda, Maryland. Tuition for the course is $250.00.

Early registration is desirable in order that students may complete assigned reading material prior to participation in the course.

Further information may be obtained from the Registrar, Georgetown University School of Dentistry, 3900 Reservoir Rd., Washington 7, D. C.

---

## Jewish Chronic Disease Hospital

Applications are being received for a one-year residency in anesthesiology for graduate dentists under Stanley R. Spiro, D.D.S., at the Jewish Chronic Disease Hospital beginning July 1, 1960. Full maintenance and a stipend of $200.00 per month are provided. Requests should be addressed to Joseph J. Obst, D.D.S., Director of Dentistry, Jewish Chronic Disease Hospital, 86 East 49th St., Brooklyn 3, New York.

# REVIEWS OF THE LITERATURE

## ABSTRACTS OF CURRENT LITERATURE

**Some Thoughts on Hemophilias and Pseudohemophilias.** Rudof Marx. München. med. Wchnschr. **101**: 881-924, 1959.

There are two types of recessive, hereditary hemophilia. They are grouped as hemophilia types A and B according to the absence of two different plasma proteins necessary for blood thrombokinase production.

The author's studies included seventy-one men who had recessive sex-linked type A hemophilia and seventeen with disorders categorized as pseudohemophilia type B. The incidence was estimated as one patient with type A hemophilia per 10,000 men and one with type B per 100,000 men.

Multiple therapeutic measures are described.

**Pre-anesthetic Medication; Old and New Concepts.** J. Adriani and D. H. Yarberry. A. M. A. Arch. Surg. **79**: 128, December, 1959.

Why give premedication? What are the criteria for selection of premedication? What drugs are used? These questions and many others are answered. The article is designated as "surgery illustrated." It was shown as a scientific exhibit of the section on anesthesiology at the 108th annual meeting of the American Medical Association in Atlantic City, June 8 to 12, 1956.

This article is recommended reading for the oral surgeon.

**Headache Caused by Bruxism.** Woodrow S. Monico. Ann. Otol., Phin. & Laryng. **68**: 1159, December, 1959.

Sustained contractions of the temporal muscles can cause disagreeable head pains. In abnormal mouth habits, such as bruxism, the teeth are forcefully ground against each other for prolonged periods. Bruxism is caused by malocclusion.

**Tumors of the Parotid Glands.** O. H. Bears, K. D. Devine, L. B. Wollner, and A. H. Bulbulian. A. M. A. Arch. Surg. **79**: 52, December, 1959.

"Mixed tumors" in the parotid gland comprise 80 per cent of the benign tumors. Long-standing mixed tumors may undergo malignant transformations, and recurrent lesions are usually multicentric.

Warthin's tumor makes up 7 per cent of the benign group and occurs predominantly in male patients.

Mikulicz's disease is a rare condition found in one or more of the salivary glands.

In the malignant group, cylindroma, acini-cell carcinoma, and mucoepidermoid carcinoma are considered moderately malignant, while highly malignant tumors include

squamous-cell carcinoma, adenocarcinoma, and undifferentiated carcinoma. Surgical management with parotidectomy is recommended.

The article is recommended to the oral surgeon.

T. J. C.

**Fluothane: A New Nonexplosive Volatile Anesthetic Agent—Preliminary Report on 2,000 Administrations.** H. M. Ausherman and A. Adan. South. M. J. 52: 46, January, 1959.

Fluothane was used as the principal anesthetic agent for 2,000 unselected patients of all ages.

Fluothane offers several advantages: It is nonirritating to the respiratory tract; it inhibits salivary and bronchial secretions; it is not unpleasant to inhale; induction and recovery are rapid; it is nonexplosive; respirations can be controlled easily; and there is less postoperative vomiting.

Its disadvantages are that it may cause arrhythmias; it is incompatible with epinephrine; and it depresses the respiration and the cardiovascular system.

**The Treatment of Fractures.** L. F. Peltier. Surg. Gynec. & Obst. 109: 376, September, 1959.

The object of treatment is to restore normal function with solid union and without obvious deformity. The problem is how best to achieve this object. The solution lies not in a sterile debate over the value of closed methods versus operative methods of treatment but in a consideration of how the surgeon can best obtain the most satisfactory result for a particular patient with a particular injury. Just as the fractures themselves are infinitely varied, so must their treatment be thoughtfully individualized.

Both closed and operative methods of treating fractures demand the same degree of judgment and skill for their proper execution. Some surgeons are reluctant to perform operative procedures on patients with fractures because of lack of training or experience, while others rely heavily upon operative methods because they are unable to use closed methods of treatment effectively. Good results are most consistently realized by the surgeon who is the master of both methods.